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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/DK00/00264  <b>(22) International Filing Date:</b> 16 May 2000 (16.05.00)  <b>(30) Priority Data:</b> PA 1999 00684 17 May 1999 (17.05.99) DK PA 2000 00478 21 March 2000 (21.03.00) DK  <b>(71) Applicants:</b> NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsværd (DK). AGOURON PHARMACEUTI- CALS, INC. [US/US]; 10350 North Torrey Pines Road, La Jolla, CA 92037 (US).		<b>(72) Inventors:</b> LING, Anthony; 10933 Caminito Cuesta, San Diego, CA 92131 (US). PLEWE, Michael, Bruno; Caminito Eva 4711, San Diego, CA 92130 (US). TRUESDALE, Larry, Kenneth; 10382 Rue Chamberly, San Diego, CA 92131 (US). LAU, Jesper; Rosenvænget 3, DK-3520 Farum (DK). MADSEN, Peter; Ulvejbjerg 7, DK-2880 Bagsværd (DK). SAMS, Christian; Jakob Danneferds Vej 4a 1., DK-1973 Frederiksberg C (DK). BEHRENS, Carsten; Lundtoftegade 107, 1.th., DK-2200 Copenhagen N (DK). VAGNER, Josef; 12381 N. Granville Canyon Way, Oro Valley, AZ 85737 (US). CHRISTENSEN, Inge, Thøger; Kulsviertofte 52, DK-2800 Lyngby (DK). LUNDT, Behrend, Frederik; Rosenhaven 118, DK-2980 Kokkedal (DK). SIDELMANN, Ulla, Grove; Dronningeen- gen 10A, DK-2950 Vedbæk (DK). THØGERSEN, Hen- ning; Gregersmindevej 8, DK-3520 Farum (DK).  <b>(81) Designated States:</b> AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> GLUCAGON ANTAGONISTS/INVERSE AGONISTS  <b>(57) Abstract</b>  A novel class of compounds, which act to antagonize the action of the glucagon hormone on the glucagon receptor. Owing to their antagonizing effect of the glucagon receptor the compounds may be suitable for the treatment and/or prevention of any glucagon-mediated conditions and diseases such as hyperglycemia, Type 1 diabetes, Type 2 diabetes and obesity.		

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## GLUCAGON ANTAGONISTS/INVERSE AGONISTS

### FIELD OF THE INVENTION

- 5 The present invention relates to agents that act to antagonize the action of the glucagon peptide hormone. More particularly, it relates to glucagon antagonists or inverse agonists.

### BACKGROUND OF THE INVENTION

- 10 Glucagon is a key hormonal agent that, in co-operation with insulin, mediates homeostatic regulation of the amount of glucose in the blood. Glucagon primarily acts by stimulating certain cells (mostly liver cells) to release glucose when blood glucose levels fall. The action of glucagon is opposite to that of insulin, which stimulates cells to take up and store glucose whenever blood glucose levels rise. Both glucagon and insulin are peptide hormones.

15

- Glucagon is produced in the alpha islet cells of the pancreas and insulin in the beta islet cells. Diabetes mellitus is a common disorder of glucose metabolism. The disease is characterized by hyperglycemia and may be classified as Type 1 diabetes, the insulin-dependent form, or Type 2 diabetes, which is non-insulin-dependent in character. Subjects with Type 1 diabetes are hyperglycemic and hypoinsulinemic, and the conventional treatment for this form of the disease is to provide insulin. However, in some patients with Type 1 or Type 2 diabetes, absolute or relative elevated glucagon levels have been shown to contribute to the hyperglycemic state. Both in healthy control animals as well as in animal models of Type 1 and Type 2 diabetes, removal of circulating glucagon with selective and specific antibodies has resulted in reduction of the glycemic level (Brand et al., Diabetologia 37, 985 (1994); Diabetes 43, [suppl 1], 172A (1994); Am. J. Physiol. 269, E469-E477 (1995); Diabetes 44 [suppl 1], 134A (1995); Diabetes 45, 1076 (1996)). These studies suggest that glucagon suppression or an action that antagonizes glucagon could be a useful adjunct to conventional antihyperglycemia treatment of diabetes. The action of glucagon can be suppressed by providing an antagonist or an inverse agonist, ie substances that inhibit or prevent glucagon induced responses. The antagonist can be peptidic or non-peptidic in nature. Native glucagon is a 29 amino acid peptide having the sequence:
- 20  
25  
30

His-Ser-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr-NH<sub>2</sub>.

35

Glucagon exerts its action by binding to and activating its receptor, which is part of the Glucagon-Secretin branch of the 7-transmembrane G-protein coupled receptor family (Jelinek et

al., Science 259, 1614, (1993)). The receptor functions by an activation of the adenylyl cyclase second messenger system and the result is an increase in cAMP levels.

Several publications disclose peptides that are stated to act as glucagon antagonists. Probably, the most thoroughly characterized antagonist is DesHis<sup>1</sup>[Glu<sup>9</sup>]-glucagon amide (Unson et al., Peptides 10, 1171 (1989); Post et al., Proc. Natl. Acad. Sci. USA 90, 1662 (1993)). Other antagonists are eg DesHis<sup>1</sup>,Phe<sup>6</sup>[Glu<sup>9</sup>]-glucagon amide (Azizh et al., Bioorganic & Medicinal Chem. Lett. 16, 1849 (1995)) or NLeu<sup>9</sup>,Ala<sup>11,18</sup>-glucagon amide (Unson et al., J. Biol. Chem. 269(17), 12548 (1994)).

Peptide antagonists of peptide hormones are often quite potent; however, they are generally known not to be orally available because of degradation by physiological enzymes, and poor distribution in vivo. Therefore, orally available non-peptide antagonists of the peptide hormones are preferred. Among the non-peptide glucagon antagonists, a quinoxaline derivative, (2-styryl-3-[3-(dimethylamino)propylmethylamino]-6,7-dichloroquinoxaline was found to displace glucagon from the rat liver receptor (Collins, J.L. et al., Bioorganic and Medicinal Chemistry Letters 2(9):915-918 (1992)). West, R.R. et al., WO 94/14426 (1994) discloses use of skyrin, a natural product comprising a pair of linked 9,10-anthracenedione groups, and its synthetic analogues, as glucagon antagonists. Anderson, P.L., US patent No. 4,359,474 discloses the glucagon antagonistic properties of 1-phenyl pyrazole derivatives. Barcza, S., U.S. Patent No. 4,374,130, discloses substituted disilacyclohexanes as glucagon antagonists. WO 98/04528 (Bayer Corporation) discloses substituted pyridines and biphenyls as glucagon antagonists. WO 97/16442 and US patent No 5,776,954 (Merck & Co., Inc.) disclose substituted pyridyl pyrroles as glucagon antagonists and WO 98/21957, WO 98/22108, WO 98/22109 and US 5,880,139 (Merck & Co., Inc.) disclose 2,4-diaryl-5-pyridylimidazoles as glucagon antagonists. Furthermore, WO 97/16442, US patent Nos 5,837,719 and 5,776,954 (Merck & Co., Inc.) discloses 2,5-substituted aryl pyrroles as glucagon antagonists. WO 98/24780, WO 98/24782, WO 99/24404 and WO 99/32448 (Amgen Inc.) disclose substituted pyrimidinone and pyridone compounds and substituted pyrimidine compounds, respectively, which are stated to possess glucagon antagonistic activity. Madsen et al (J. Med. Chem. 1998 (41) 5151-7) discloses a series of 2-(benzimidazol-2-ylthio)-1-(3,4-dihydroxyphenyl)-1-ethanones as competitive human glucagon receptor antagonists. WO 99/01423 (Novo Nordisk A/S) discloses a series of acylhydrazones as glucagon antagonists/inverse agonists.

These known glucagon antagonists differ structurally from the present compounds.

**DEFINITIONS**

The following is a detailed definition of the terms used to describe the compounds of the invention:

"Halogen" designates an atom selected from the group consisting of F, Cl, Br or I.

The term "C<sub>1-6</sub>-alkyl" in the present context designates a branched or straight hydrocarbon group having from 1 to 6 carbon atoms. Representative examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, n-hexyl, isohexyl and the like.

The term "C<sub>2-6</sub>-alkenyl" as used herein represents a branched or straight hydrocarbon group having from 2 to 6 carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, iso-propenyl, 1,3-butadienyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl and the like.

The term "C<sub>2-6</sub>-alkynyl" as used herein represents a branched or straight hydrocarbon group having from 2 to 6 carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentylnyl, 2-pentylnyl, 3-pentylnyl, 4-pentylnyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 5-hexynyl, 2,4-hexadiynyl and the like.

The term "C<sub>1-6</sub>-alkoxy" as used herein, alone or in combination, refers to the radical -O-C<sub>1-6</sub>-alkyl where C<sub>1-6</sub>-alkyl is as defined above. Representative examples are methoxy, ethoxy, n-propoxy, isopropoxy, butoxy, sec-butoxy, tert-butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy and the like.

The term "C<sub>1-6</sub>-alkanoyl" as used herein denotes a group -C(O)H or -C(O)-C<sub>1-5</sub>-alkyl. Representative examples are formyl, acetyl, propionyl, butyryl, valeryl, hexanoyl and the like.

The term "C<sub>3-8</sub>-cycloalkyl" as used herein represents a carbocyclic group having from 3 to 8 carbon atoms. Representative examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

5 The term "C<sub>3-8</sub>-cycloalkenyl" as used herein represents a carbocyclic group having from 3 to 8 carbon atoms containing a least one double bond. Representative examples are 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 2-cycloheptenyl, 3-cycloheptenyl, 2-cyclooctenyl, 1,4-cyclooctadienyl and the like.

10

The term "C<sub>4-8</sub>-cycloalkenyl" as used herein represents a carbocyclic group having from 4 to 8 carbon atoms containing a least one double bond. Representative examples are 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 2-cycloheptenyl, 3-cycloheptenyl, 2-cyclooctenyl, 1,4-cyclooctadienyl and the like.

15

The term "heterocyclyl" as used herein represents a saturated or partially unsaturated 3 to 10 membered ring containing one or more heteroatoms selected from nitrogen, oxygen and sulfur. Representative examples are pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, aziridinyl, tetrahydrofuranyl and the like.

20

The term "aryl" as used herein is intended to include carbocyclic aromatic ring systems such as phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, pentalenyl, azulenyl, and the like. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems enumerated above. Non-limiting examples of such partially hydro-

25 generated derivatives are 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl and the like.

The term "aryloxy" as used herein denotes a group -O-aryl, wherein aryl is as defined above.

The term "aroyl" as used herein denotes a group -C(O)-aryl, wherein aryl is as defined above.

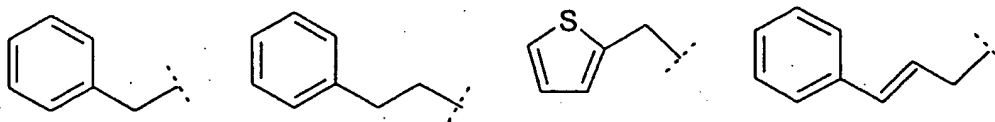
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The term "heteroaryl" as used herein is intended to include heterocyclic aromatic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulfur such as furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-

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thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothieryl, benzothiophenyl (thianaphthenyl), indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinoliziny, quinolinyl, isoquinolinyl, quinoxaliny, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl and the like. Heteroaryl is also intended to include the partially hydrogenated derivatives of the heterocyclic systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 2,3-dihydrobenzofuranyl, pyrrolinyl, pyrazolinyl, indolinyl, oxazolidinyl, oxazolinyl, oxazepinyl and the like.

10 "Aryl-C<sub>1-6</sub>-alkyl", "heteroaryl-C<sub>1-6</sub>-alkyl", "aryl-C<sub>2-6</sub>-alkenyl" etc. mean C<sub>1-6</sub>-alkyl or C<sub>2-6</sub>-alkenyl as defined above, substituted by an aryl or heteroaryl as defined above, for example:



The term "optionally substituted" as used herein means that the groups in question are either unsubstituted or substituted with one or more of the substituents specified. When the groups in question are substituted with more than one substituent the substituents may be the same or different.

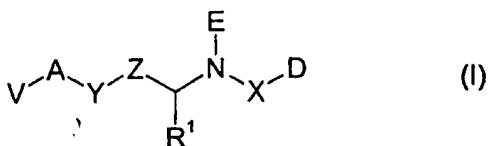
Certain of the above defined terms may occur more than once in the structural formulae, and upon such occurrence each term shall be defined independently of the other.

Furthermore, when using the terms "independently are" and "independently selected from" it should be understood that the groups in question may be the same or different.

25 The present invention is based on the unexpected observation that the compounds of the general formula (I) disclosed below antagonize the action of glucagon.

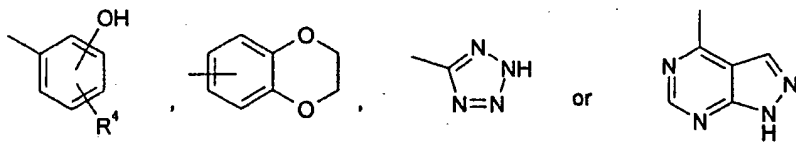
## DESCRIPTION OF THE INVENTION

Accordingly, the invention is concerned with compounds of the general formula (I):



wherein

V is  $-\text{C}(\text{O})\text{OR}^2$ ,  $-\text{C}(\text{O})\text{NR}^2\text{R}^3$ ,  $-\text{C}(\text{O})\text{NR}^2\text{OR}^3$ ,  $-\text{S}(\text{O})_2\text{OR}^2$ ,



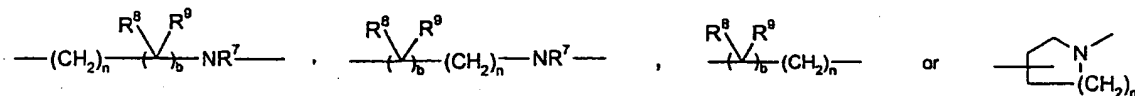
wherein

$\text{R}^2$  and  $\text{R}^3$  independently are hydrogen or  $\text{C}_{1-6}$ -alkyl,

$\text{R}^4$  is hydrogen, halogen,  $-\text{CN}$ ,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ ,  $-\text{NO}_2$ ,  $-\text{OR}^5$ ,  $-\text{NR}^5\text{R}^6$  or  $\text{C}_{1-6}$ -alkyl,

wherein  $\text{R}^5$  and  $\text{R}^6$  independently are hydrogen or  $\text{C}_{1-6}$ -alkyl,

A is



wherein

b is 0 or 1,

n is 0, 1, 2 or 3,

7

$R^7$  is hydrogen,  $C_{1-6}$ -alkyl or  $C_{3-8}$ -cycloalkyl- $C_{1-6}$ -alkyl,

$R^8$  and  $R^9$  independently are hydrogen or  $C_{1-6}$ -alkyl,

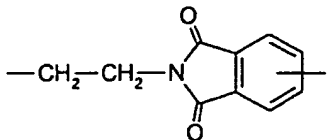
5 Y is  $-C(O)-$ ,  $-S(O)_2-$ ,  $-O-$  or a valence bond,

Z is phenylene or a divalent radical derived from a 5 or 6 membered heteroaromatic ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur,

10 which may optionally be substituted with one or two groups  $R^{46}$  and  $R^{47}$  selected from hydrogen, halogen,  $-CN$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-NO_2$ ,  $-OR^{10}$ ,  $-NR^{10}R^{11}$  and  $C_{1-6}$ -alkyl,

wherein  $R^{10}$  and  $R^{11}$  independently are hydrogen or  $C_{1-6}$ -alkyl,

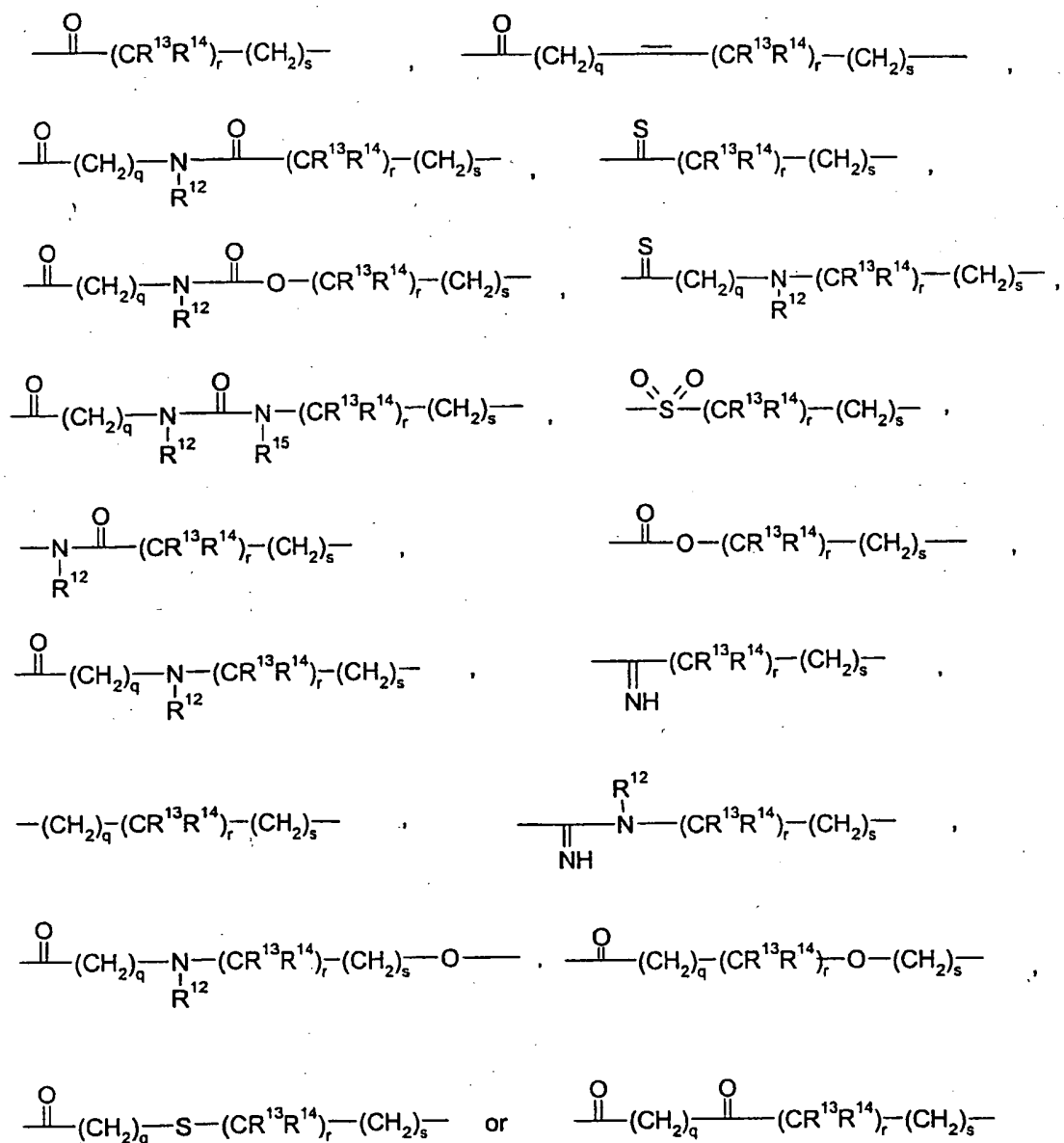
or -A-Y-Z- together are



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$R^1$  is hydrogen or  $C_{1-6}$ -alkyl,

X is



5 wherein

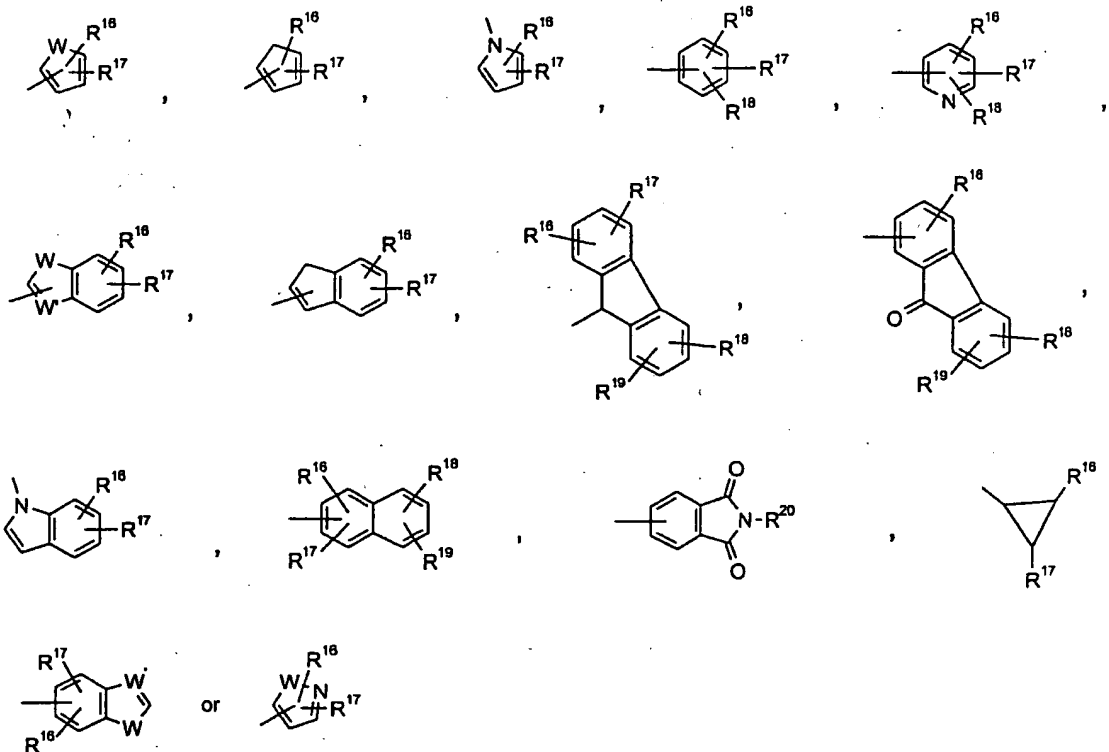
r is 0 or 1,

q and s independently are 0, 1, 2 or 3,



$R^{12}$ ,  $R^{13}$ ,  $R^{14}$  and  $R^{15}$  independently are hydrogen or  $C_{1-6}$ -alkyl,

D is



wherein

W is  $-O-$ ,  $-S-$ ,  $-S(O)_2-$  or  $-NR^{20}-$ ,

W' is  $=CR^{20}-$  or  $=N-$ ,

$R^{16}$ ,  $R^{17}$ ,  $R^{18}$  and  $R^{19}$  independently are

- hydrogen, halogen,  $-CN$ ,  $-CH_2CN$ ,  $-CHF_2$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2CF_3$ ,  $-OCF_2CHF_2$ ,  $-OS(O)_2CF_3$ ,  $-SCF_3$ ,  $-NO_2$ ,  $-OR^{21}$ ,  $-NR^{21}R^{22}$ ,  $-SR^{21}$ ,  $-NR^{21}S(O)_2R^{22}$ ,  $-S(O)_2NR^{21}R^{22}$ ,  $-S(O)NR^{21}R^{22}$ ,  $-S(O)R^{21}$ ,  $-S(O)_2R^{21}$ ,  $-OS(O)_2R^{21}$ ,  $-C(O)NR^{21}R^{22}$ ,  $-OC(O)NR^{21}R^{22}$ ,  $-NR^{21}C(O)R^{22}$ ,  $-CH_2C(O)NR^{21}R^{22}$ ,  $-OCH_2C(O)NR^{21}R^{22}$ ,  $-CH_2OR^{21}$ ,  $-CH_2NR^{21}R^{22}$ ,  $-OC(O)R^{21}$ ,  $-C(O)R^{21}$  or  $-C(O)OR^{21}$ ,

- C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl or C<sub>2-6</sub>-alkynyl,

which may optionally be substituted with one or more substituents selected from -  
 CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -SCF<sub>3</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>,  
 -SR<sup>21</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, -OC(O)NR<sup>21</sup>R<sup>22</sup>, -NR<sup>21</sup>C(O)R<sup>22</sup>,  
 -OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -C(O)R<sup>21</sup> and -C(O)OR<sup>21</sup>,

- C<sub>3-8</sub>-cycloalkyl, C<sub>4-8</sub>-cycloalkenyl, heterocyclyl, C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkyl, C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkoxy, C<sub>3-8</sub>-cycloalkyloxy, C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkylthio, C<sub>3-8</sub>-cycloalkylthio, C<sub>3-8</sub>-cycloalkyl-C<sub>2-6</sub>-alkenyl, C<sub>3-8</sub>-cycloalkyl-C<sub>2-6</sub>-alkynyl, C<sub>4-8</sub>-cycloalkenyl-C<sub>1-6</sub>-alkyl, C<sub>4-8</sub>-cycloalkenyl-C<sub>2-6</sub>-alkenyl, C<sub>4-8</sub>-cycloalkenyl-C<sub>2-6</sub>-alkynyl, heterocyclyl-C<sub>1-6</sub>-alkyl, heterocyclyl-C<sub>2-6</sub>-alkenyl or heterocyclyl-C<sub>2-6</sub>-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from

-CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -SCF<sub>3</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>,  
 -SR<sup>21</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, -OC(O)NR<sup>21</sup>R<sup>22</sup>, -NR<sup>21</sup>C(O)R<sup>22</sup>,  
 -OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -C(O)R<sup>21</sup> and -C(O)OR<sup>21</sup>,

C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl and C<sub>2-6</sub>-alkynyl,

which may optionally be substituted with one or more substituents selected from -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>,  
 -SCF<sub>3</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>, -SR<sup>21</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>,  
 -OC(O)NR<sup>21</sup>R<sup>22</sup>, -NR<sup>21</sup>C(O)R<sup>22</sup>, -OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -C(O)R<sup>21</sup> and -C(O)OR<sup>21</sup>,

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C<sub>1-6</sub>-alkoxy, aryl-C<sub>1-6</sub>-alkyl, aryl-C<sub>2-6</sub>-alkenyl, aryl-C<sub>2-6</sub>-alkynyl, heteroaryl, heteroaryl-C<sub>1-6</sub>-alkyl, heteroaryl-C<sub>2-6</sub>-alkenyl or heteroaryl-C<sub>2-6</sub>-alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from

halogen, -CN, -CH<sub>2</sub>CN, -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>,  
 -OS(O)<sub>2</sub>CF<sub>3</sub>, -SCF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>, -SR<sup>21</sup>, -NR<sup>21</sup>S(O)<sub>2</sub>R<sup>22</sup>, -S(O)<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>,  
 -S(O)NR<sup>21</sup>R<sup>22</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -OS(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, -OC(O)NR<sup>21</sup>R<sup>22</sup>,  
 -NR<sup>21</sup>C(O)R<sup>22</sup>, -CH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -CH<sub>2</sub>OR<sup>21</sup>, -CH<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>,  
 -OC(O)R<sup>21</sup>, -C(O)R<sup>21</sup> and -C(O)OR<sup>21</sup>,

C<sub>1-8</sub>-alkyl, C<sub>2-8</sub>-alkenyl and C<sub>2-8</sub>-alkynyl,

which may optionally be substituted with one or more substituents selected from -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>,  
 -SCF<sub>3</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>, -SR<sup>21</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>,  
 -OC(O)NR<sup>21</sup>R<sup>22</sup>, -NR<sup>21</sup>C(O)R<sup>22</sup>, -OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -C(O)R<sup>21</sup> and  
 -C(O)OR<sup>21</sup>,

wherein R<sup>21</sup> and R<sup>22</sup> independently are hydrogen, -CF<sub>3</sub>, C<sub>1-8</sub>-alkyl, tri-C<sub>1-8</sub>-alkylsilyl, C<sub>3-8</sub>-cycloalkyl, C<sub>3-8</sub>-cycloalkyl-C<sub>1-8</sub>-alkyl, aryl, aryl-C<sub>1-8</sub>-alkyl or heteroaryl,

or R<sup>21</sup> and R<sup>22</sup> when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R<sup>18</sup> to R<sup>19</sup> when placed in adjacent positions together may form a bridge  
 -(CR<sup>18</sup>R<sup>17</sup>)<sub>a</sub>-O-(CR<sup>18</sup>R<sup>19</sup>)<sub>c</sub>-O-

wherein

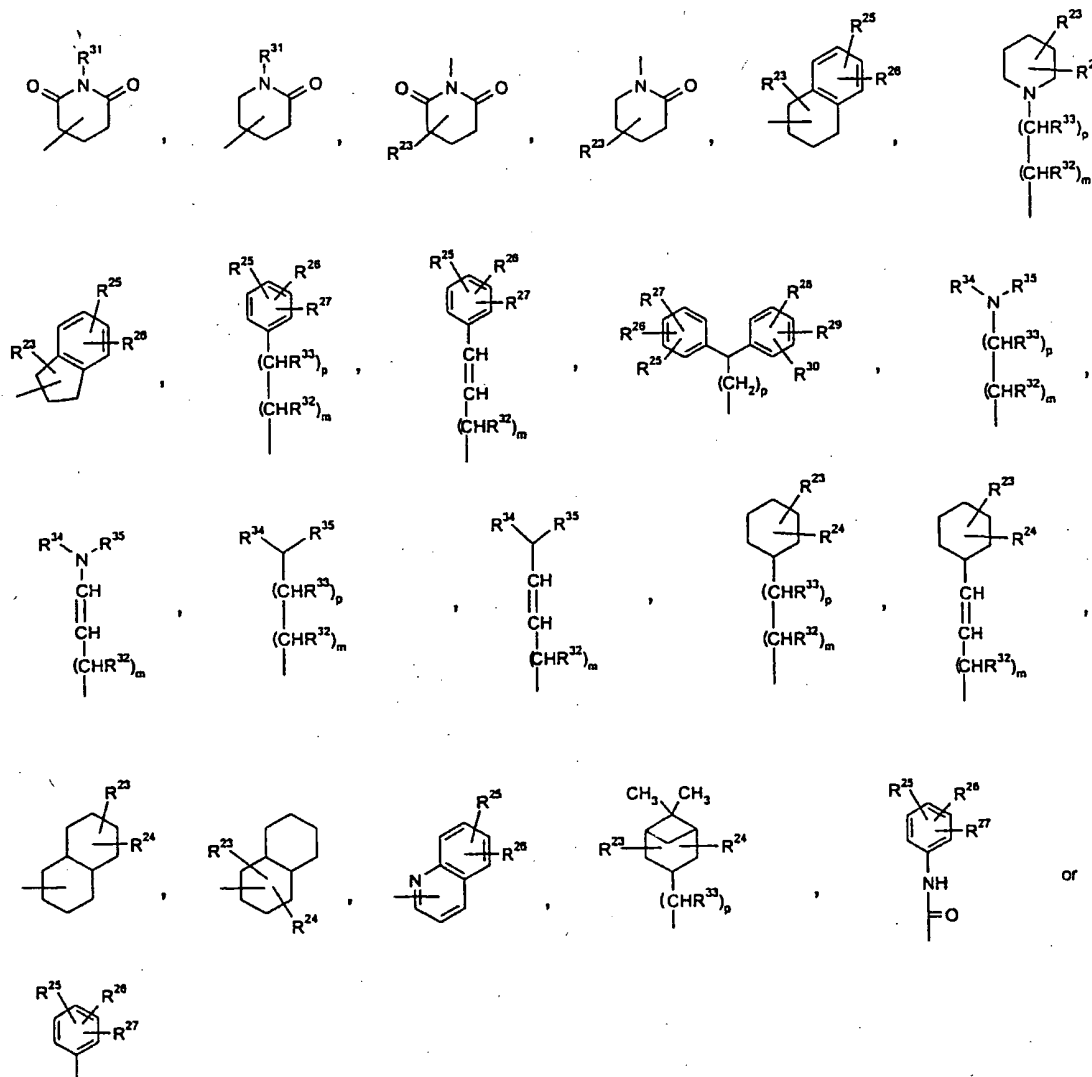
a is 0, 1 or 2,

c is 1 or 2,

R<sup>18</sup>, R<sup>17</sup>, R<sup>18</sup> and R<sup>19</sup> independently are hydrogen, C<sub>1-8</sub>-alkyl or halogen,

R<sup>20</sup> and R<sup>20</sup> independently are hydrogen, C<sub>1-8</sub>-alkyl, C<sub>3-8</sub>-cycloalkyl or C<sub>3-8</sub>-cycloalkyl-C<sub>1-8</sub>-alkyl,

- E is a 3 to 9 membered mono- or bicyclic ring which may optionally contain one or two double bonds and which may optionally contain one or two heteroatoms selected from nitrogen, oxygen and sulfur, wherein one or two groups  $R^{23}$  and  $R^{24}$  may be attached to the same or different ring carbon atoms and wherein a group  $R^{31}$  may be attached to a ring nitrogen atom when present, or



wherein

10

m and p independently are 0, 1, 2, 3 or 4, with the proviso that when both m and p are present in the same formula at least one of m and p is different from 0,

R<sup>23</sup> and R<sup>24</sup> independently are

- hydrogen, -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -SCF<sub>3</sub>, -OR<sup>36</sup>, -NR<sup>36</sup>R<sup>37</sup>,  
 5 -SR<sup>36</sup>, -S(O)R<sup>36</sup>, -S(O)<sub>2</sub>R<sup>36</sup>, -C(O)NR<sup>36</sup>R<sup>37</sup>, -OC(O)NR<sup>36</sup>R<sup>37</sup>, -NR<sup>36</sup>C(O)R<sup>37</sup>,  
 -OCH<sub>2</sub>C(O)NR<sup>36</sup>R<sup>37</sup>, -C(O)R<sup>36</sup> or -C(O)OR<sup>36</sup>,

- C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl or C<sub>2-6</sub>-alkynyl,

10 which may optionally be substituted with one or more substituents selected from  
 -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -SCF<sub>3</sub>, -OR<sup>36</sup>, -NR<sup>36</sup>R<sup>37</sup>,  
 -SR<sup>36</sup>, -S(O)R<sup>36</sup>, -S(O)<sub>2</sub>R<sup>36</sup>, -C(O)NR<sup>36</sup>R<sup>37</sup>, -OC(O)NR<sup>36</sup>R<sup>37</sup>, -NR<sup>36</sup>C(O)R<sup>37</sup>,  
 -OCH<sub>2</sub>C(O)NR<sup>36</sup>R<sup>37</sup>, -C(O)R<sup>36</sup> and -C(O)OR<sup>36</sup>,

- 15 • C<sub>3-8</sub>-cycloalkyl, C<sub>3-8</sub>-cycloalkylidene, C<sub>4-8</sub>-cycloalkenyl, heterocyclyl, C<sub>3-8</sub>-cycloalkyl-  
 C<sub>1-6</sub>-alkyl, C<sub>3-8</sub>-cycloalkyl-C<sub>2-6</sub>-alkenyl, C<sub>3-8</sub>-cycloalkyl-C<sub>2-6</sub>-alkynyl, C<sub>4-8</sub>-cycloalkenyl-  
 C<sub>1-6</sub>-alkyl, C<sub>4-8</sub>-cycloalkenyl-C<sub>2-6</sub>-alkenyl, C<sub>4-8</sub>-cycloalkenyl-C<sub>2-6</sub>-alkynyl, heterocyclyl-  
 C<sub>1-6</sub>-alkyl, heterocyclyl-C<sub>2-6</sub>-alkenyl or heterocyclyl-C<sub>2-6</sub>-alkynyl,

20 of which the cyclic moieties optionally may be substituted with one or more sub-  
 stituents selected from

- CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -SCF<sub>3</sub>, -OR<sup>36</sup>, -NR<sup>36</sup>R<sup>37</sup>,  
 -SR<sup>36</sup>, -S(O)R<sup>36</sup>, -S(O)<sub>2</sub>R<sup>36</sup>, -C(O)NR<sup>36</sup>R<sup>37</sup>, -OC(O)NR<sup>36</sup>R<sup>37</sup>, -NR<sup>36</sup>C(O)R<sup>37</sup>,  
 25 -OCH<sub>2</sub>C(O)NR<sup>36</sup>R<sup>37</sup>, -C(O)R<sup>36</sup> and -C(O)OR<sup>36</sup>,

C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl and C<sub>2-6</sub>-alkynyl,

30 which may optionally be substituted with one or more substituents se-  
 lected from -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>,  
 -SCF<sub>3</sub>, -OR<sup>36</sup>, -NR<sup>36</sup>R<sup>37</sup>, -SR<sup>36</sup>, -S(O)R<sup>36</sup>, -S(O)<sub>2</sub>R<sup>36</sup>, -C(O)NR<sup>36</sup>R<sup>37</sup>,  
 -OC(O)NR<sup>36</sup>R<sup>37</sup>, -NR<sup>36</sup>C(O)R<sup>37</sup>, -OCH<sub>2</sub>C(O)NR<sup>36</sup>R<sup>37</sup>, -C(O)R<sup>36</sup> and  
 -C(O)OR<sup>36</sup>,

- aryl, aryloxy, aroyl, aryl-C<sub>1-6</sub>-alkoxy, aryl-C<sub>1-6</sub>-alkyl, aryl-C<sub>2-6</sub>-alkenyl, aryl-C<sub>2-6</sub>-alkynyl, heteroaryl, heteroaryl-C<sub>1-6</sub>-alkyl, heteroaryl-C<sub>2-6</sub>-alkenyl or heteroaryl-C<sub>2-6</sub>-alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from

halogen, -CN, -CH<sub>2</sub>CN, -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -OS(O)<sub>2</sub>CF<sub>3</sub>, -SCF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>36</sup>, -NR<sup>36</sup>R<sup>37</sup>, -SR<sup>36</sup>, -NR<sup>36</sup>S(O)<sub>2</sub>R<sup>37</sup>, -S(O)<sub>2</sub>NR<sup>36</sup>R<sup>37</sup>, -S(O)NR<sup>36</sup>R<sup>37</sup>, -S(O)R<sup>36</sup>, -S(O)<sub>2</sub>R<sup>36</sup>, -OS(O)<sub>2</sub>R<sup>36</sup>, -C(O)NR<sup>36</sup>R<sup>37</sup>, -OC(O)NR<sup>36</sup>R<sup>37</sup>, -NR<sup>36</sup>C(O)R<sup>37</sup>, -CH<sub>2</sub>C(O)NR<sup>36</sup>R<sup>37</sup>, -CH<sub>2</sub>C(O)NR<sup>36</sup>R<sup>37</sup>, -CH<sub>2</sub>OR<sup>36</sup>, -CH<sub>2</sub>NR<sup>36</sup>R<sup>37</sup>, -OC(O)R<sup>36</sup>, -C(O)R<sup>36</sup> and -C(O)OR<sup>36</sup>,

C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl and C<sub>2-6</sub>-alkynyl,

which may optionally be substituted with one or more substituents selected from -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -SCF<sub>3</sub>, -OR<sup>36</sup>, -NR<sup>36</sup>R<sup>37</sup>, -SR<sup>36</sup>, -S(O)R<sup>36</sup>, -S(O)<sub>2</sub>R<sup>36</sup>, -C(O)NR<sup>36</sup>R<sup>37</sup>, -OC(O)NR<sup>36</sup>R<sup>37</sup>, -NR<sup>36</sup>C(O)R<sup>37</sup>, -OCH<sub>2</sub>C(O)NR<sup>36</sup>R<sup>37</sup>, -C(O)R<sup>36</sup> and -C(O)OR<sup>36</sup>,

wherein R<sup>36</sup> and R<sup>37</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl or aryl,

of which the aryl moiety optionally may be substituted with one or more substituents selected from halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>38</sup>, -NR<sup>38</sup>R<sup>39</sup> and C<sub>1-6</sub>-alkyl,

wherein R<sup>38</sup> and R<sup>39</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl,

or R<sup>36</sup> and R<sup>37</sup> when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or R<sup>23</sup> and R<sup>24</sup> when attached to the same ring carbon atom or different ring carbon atoms together may form a radical -O-(CH<sub>2</sub>)<sub>t</sub>-CR<sup>40</sup>R<sup>41</sup>-(CH<sub>2</sub>)<sub>t</sub>-O-, -(CH<sub>2</sub>)<sub>t</sub>-CR<sup>40</sup>R<sup>41</sup>-(CH<sub>2</sub>)<sub>t</sub>- or



wherein

5 t and l independently are 0, 1, 2, 3, 4 or 5,

$R^{40}$  and  $R^{41}$  independently are hydrogen or  $C_{1-6}$ -alkyl,

$R^{25}$  to  $R^{30}$  independently are hydrogen, halogen, -CN, -CF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>42</sup>, -NR<sup>42</sup>R<sup>43</sup>,  $C_{1-6}$ -alkyl,  
10  $C_{3-8}$ -cycloalkyl or  $C_{4-8}$ -cycloalkenyl,

wherein  $R^{42}$  and  $R^{43}$  independently are hydrogen or  $C_{1-6}$ -alkyl, or

$R^{42}$  and  $R^{43}$  when attached to the same nitrogen atom together with the said nitrogen atom  
15 may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

$R^{31}$ ,  $R^{32}$  and  $R^{33}$  independently are hydrogen or  $C_{1-6}$ -alkyl,

20

$R^{34}$  and  $R^{35}$  independently are

- hydrogen,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy,  $C_{1-6}$ -alkanoyl, -C(O)NR<sup>44</sup>R<sup>45</sup> or -S(O)<sub>2</sub>R<sup>45</sup>,
- 25 • aryl, aroyl, aryl- $C_{1-6}$ -alkoxy, aryl- $C_{1-6}$ -alkanoyl or aryl- $C_{1-6}$ -alkyl,

of which the aryl moieties optionally may be substituted with one or more substituents selected from halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OR<sup>44</sup>, -NR<sup>44</sup>R<sup>45</sup> and  $C_{1-6}$ -alkyl,

30 wherein  $R^{44}$  and  $R^{45}$  independently are hydrogen or  $C_{1-6}$ -alkyl, or

$R^{34}$  and  $R^{35}$  when attached to a carbon atom together with the said carbon atom may form a 3 to 8 membered cyclic ring optionally containing one or two heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds, or

35

$R^{34}$  and  $R^{35}$  when attached to a nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds,

- 5 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

The compounds according to the invention preferably have an  $IC_{50}$  value of no greater than 5  $\mu M$  as determined by the Glucagon Binding Assay (I), Glucagon Binding Assay (II) or

- 10 Glucagon Binding Assay (III) disclosed herein.

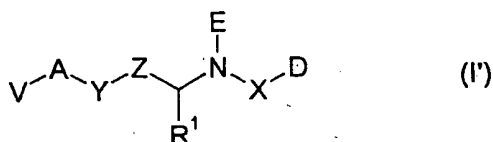
More preferably, the compounds according to the invention have a glucagon antagonistic activity as determined by the Glucagon Binding Assay (I), Glucagon Binding Assay (II) or Glucagon Binding Assay (III) disclosed herein corresponding to an  $IC_{50}$  value of less than 1  $\mu M$ ,

- 15 preferably of less than 500 nM and even more preferred of less than 100 nM.

The compounds according to the invention are useful for the treatment and/or prevention of an indication selected from the group consisting of hyperglycemia, IGT (impaired glucose tolerance), Type 2 diabetes, Type 1 diabetes and obesity.

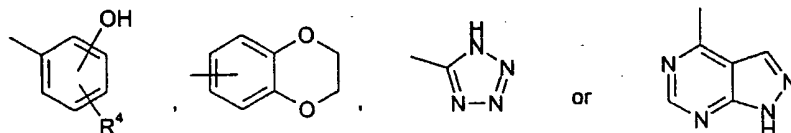
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In a further aspect the invention relates to compounds of the general formula (I'):



- 25 wherein

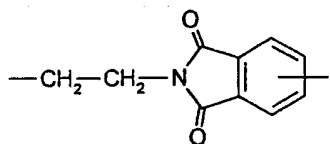
V is  $-\text{C}(\text{O})\text{OR}^2$ ,  $-\text{C}(\text{O})\text{NR}^2\text{R}^3$ ,  $-\text{C}(\text{O})\text{NR}^2\text{OR}^3$ ,



- 30 wherein

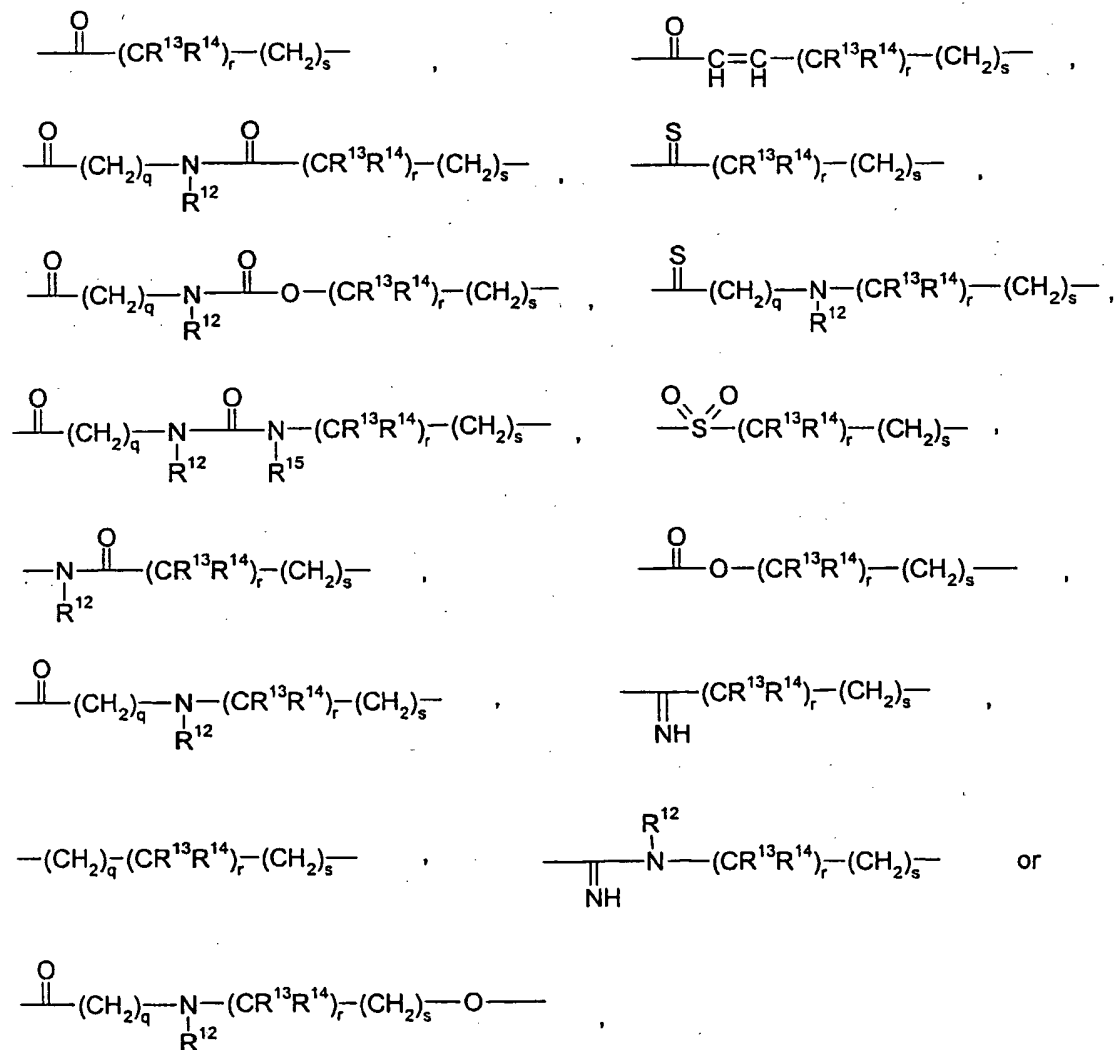






R<sup>1</sup> is hydrogen or C<sub>1-6</sub>-alkyl;

5 X is



wherein

10

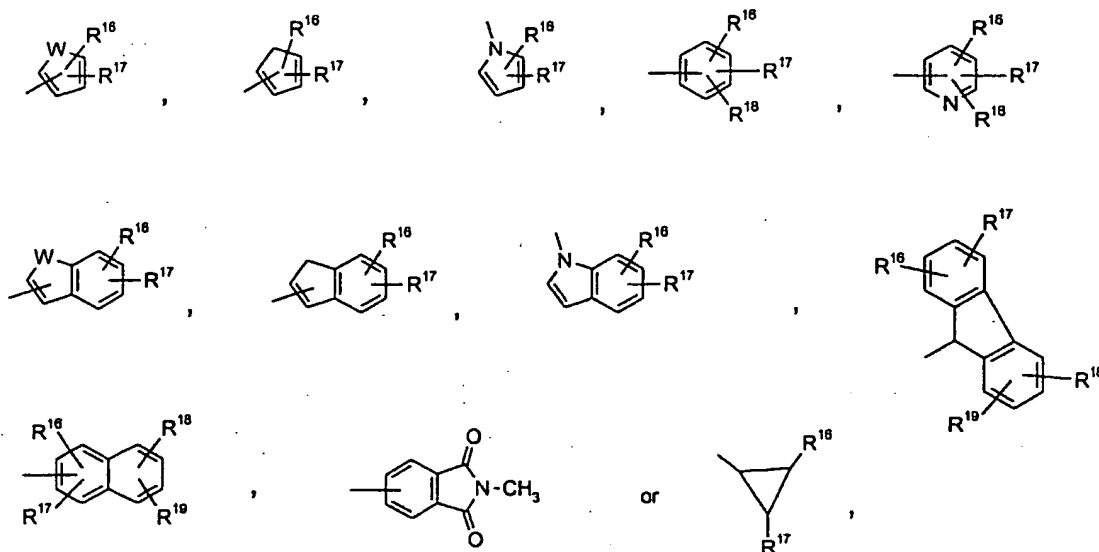
r is 0 or 1,

$q$  and  $s$  independently are 0, 1, 2 or 3,

$R^{12}$ ,  $R^{13}$ ,  $R^{14}$  and  $R^{15}$  independently are hydrogen or  $C_{1-8}$ -alkyl;

5

D is.



10 wherein

W is -O-, -S- or -NR<sup>20</sup>-,

wherein R<sup>20</sup> is hydrogen or C<sub>1-6</sub>-alkyl,

15

$R^{16}$ ,  $R^{17}$ ,  $R^{18}$  and  $R^{19}$  independently are

hydrogen, halogen, -CN, -CH<sub>2</sub>CN, -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>,  
-OS(O)<sub>2</sub>CF<sub>3</sub>, -SCF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>, -SR<sup>21</sup>, -NR<sup>21</sup>S(O)<sub>2</sub>R<sup>22</sup>, -S(O)<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>,  
20 -S(O)NR<sup>21</sup>R<sup>22</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -OS(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, -OC(O)NR<sup>21</sup>R<sup>22</sup>,  
-NR<sup>21</sup>C(O)R<sup>22</sup>, -CH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -CH<sub>2</sub>OR<sup>21</sup>, -CH<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>, -OC(O)R<sup>21</sup>,  
-C(O)R<sup>21</sup> or -C(O)OR<sup>21</sup>,

**C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl or C<sub>2-6</sub>-alkynyl,**

which may optionally be substituted with one or more substituents selected from -  
 CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -SCF<sub>3</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>,  
 -SR<sup>21</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, -OC(O)NR<sup>21</sup>R<sup>22</sup>, -NR<sup>21</sup>C(O)R<sup>22</sup>,  
 -OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -C(O)R<sup>21</sup> and -C(O)OR<sup>21</sup>,

5

C<sub>3-8</sub>-cycloalkyl, C<sub>3-8</sub>-cycloalkenyl, heterocyclyl, C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkyl,  
 C<sub>3-8</sub>-cycloalkyl-C<sub>2-6</sub>-alkenyl, C<sub>3-8</sub>-cycloalkyl-C<sub>2-6</sub>-alkynyl, C<sub>3-8</sub>-cycloalkenyl-C<sub>1-6</sub>-alkyl,  
 C<sub>3-8</sub>-cycloalkenyl-C<sub>2-6</sub>-alkenyl, C<sub>3-8</sub>-cycloalkenyl-C<sub>2-6</sub>-alkynyl, heterocyclyl-C<sub>1-6</sub>-alkyl, heterocy-  
 clyl-C<sub>2-6</sub>-alkenyl or heterocyclyl-C<sub>2-6</sub>-alkynyl,

10

of which the cyclic moieties optionally may be substituted with one or more sub-  
 stituents selected from -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>,  
 -SCF<sub>3</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>, -SR<sup>21</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>,  
 -OC(O)NR<sup>21</sup>R<sup>22</sup>, -NR<sup>21</sup>C(O)R<sup>22</sup>, -OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -C(O)R<sup>21</sup> and -C(O)OR<sup>21</sup>,

15

C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl and C<sub>2-6</sub>-alkynyl,

which may optionally be substituted with one or more substituents se-  
 lected from -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>,  
 -SCF<sub>3</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>, -SR<sup>21</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>,  
 -OC(O)NR<sup>21</sup>R<sup>22</sup>, -NR<sup>21</sup>C(O)R<sup>22</sup>, -OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -C(O)R<sup>21</sup> and  
 -C(O)OR<sup>21</sup>,

20

aryl, aryloxy, aroyl, aryl-C<sub>1-6</sub>-alkoxy, aryl-C<sub>1-6</sub>-alkyl, aryl-C<sub>2-6</sub>-alkenyl, aryl-C<sub>2-6</sub>-alkynyl, het-  
 eroaryl, heteroaryl-C<sub>1-6</sub>-alkyl, heteroaryl-C<sub>2-6</sub>-alkenyl or heteroaryl-C<sub>2-6</sub>-alkynyl,

25

of which the aryl and heteroaryl moieties optionally may be substituted with one  
 or more substituents selected from halogen, -CN, -CH<sub>2</sub>CN, -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>,  
 -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -OS(O)<sub>2</sub>CF<sub>3</sub>, -SCF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>,  
 -SR<sup>21</sup>, -NR<sup>21</sup>S(O)<sub>2</sub>R<sup>22</sup>, -S(O)<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>, -S(O)NR<sup>21</sup>R<sup>22</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>,  
 -OS(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, -OC(O)NR<sup>21</sup>R<sup>22</sup>, -NR<sup>21</sup>C(O)R<sup>22</sup>, -CH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>,  
 -OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -CH<sub>2</sub>OR<sup>21</sup>, -CH<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>, -OC(O)R<sup>21</sup>, -C(O)R<sup>21</sup> and  
 -C(O)OR<sup>21</sup>,

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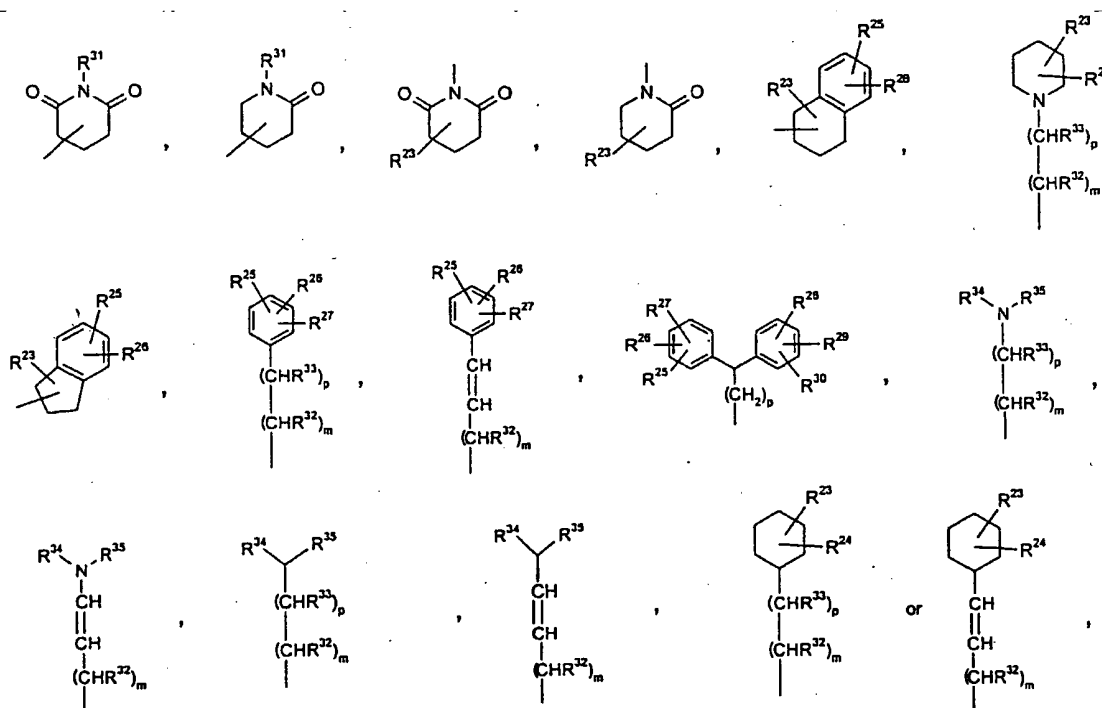
C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl and C<sub>2-6</sub>-alkynyl,

5 which may optionally be substituted with one or more substituents selected from -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -SCF<sub>3</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>, -SR<sup>21</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, -OC(O)NR<sup>21</sup>R<sup>22</sup>, -NR<sup>21</sup>C(O)R<sup>22</sup>, -OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -C(O)R<sup>21</sup> and -C(O)OR<sup>21</sup>,

10 wherein R<sup>21</sup> and R<sup>22</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl, or R<sup>21</sup> and R<sup>22</sup> when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

15 or two of the groups R<sup>18</sup> to R<sup>19</sup> when placed in adjacent positions together may form a bridge -OCH<sub>2</sub>O- or -OCH<sub>2</sub>CH<sub>2</sub>O-;

20 E is a 3 to 9 membered mono- or bicyclic ring which may optionally contain one or two double bonds and which may optionally contain one or two heteroatoms selected from nitrogen, oxygen and sulfur, wherein one or two groups R<sup>23</sup> and R<sup>24</sup> may be attached to the same or different ring carbon atoms and wherein a group R<sup>31</sup> may be attached to a ring nitrogen atom when present, or



wherein

5 m and p independently are 0, 1, 2, 3 or 4,

$R^{23}$  and  $R^{24}$  independently are hydrogen,  $-\text{CHF}_2$ ,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ ,  $-\text{OCHF}_2$ ,  $-\text{OCH}_2\text{CF}_3$ ,  $-\text{OCF}_2\text{CHF}_2$ ,  $-\text{SCF}_3$ ,  $-\text{OR}^{36}$ ,  $-\text{NR}^{36}\text{R}^{37}$ ,  $-\text{SR}^{36}$ ,  $-\text{S(O)}\text{R}^{36}$ ,  $-\text{S(O)}_2\text{R}^{36}$ ,  $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$ ,  $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{C(O)}\text{R}^{36}$  or  $-\text{C(O)}\text{OR}^{36}$ ,

10

$\text{C}_{1-8}$ -alkyl,  $\text{C}_{2-6}$ -alkenyl or  $\text{C}_{2-6}$ -alkynyl,

which may optionally be substituted with one or more substituents selected from -  
 $\text{CHF}_2$ ,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ ,  $-\text{OCHF}_2$ ,  $-\text{OCH}_2\text{CF}_3$ ,  $-\text{OCF}_2\text{CHF}_2$ ,  $-\text{SCF}_3$ ,  $-\text{OR}^{36}$ ,  $-\text{NR}^{36}\text{R}^{37}$ ,  
 15  $-\text{SR}^{36}$ ,  $-\text{S(O)}\text{R}^{36}$ ,  $-\text{S(O)}_2\text{R}^{36}$ ,  $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$ ,  
 $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{C(O)}\text{R}^{36}$  and  $-\text{C(O)}\text{OR}^{36}$ ,

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$\text{C}_{3-8}$ -cycloalkyl,  $\text{C}_{3-8}$ -cycloalkenyl, heterocyclyl,  $\text{C}_{3-8}$ -cycloalkyl- $\text{C}_{1-6}$ -alkyl,

$\text{C}_{3-8}$ -cycloalkyl- $\text{C}_{2-6}$ -alkenyl,  $\text{C}_{3-8}$ -cycloalkyl- $\text{C}_{2-6}$ -alkynyl,  $\text{C}_{3-8}$ -cycloalkenyl- $\text{C}_{1-6}$ -alkyl,

20

$\text{C}_{3-8}$ -cycloalkenyl- $\text{C}_{2-6}$ -alkenyl,  $\text{C}_{3-8}$ -cycloalkenyl- $\text{C}_{2-6}$ -alkynyl, heterocyclyl- $\text{C}_{1-6}$ -alkyl, heterocyclyl- $\text{C}_{2-6}$ -alkenyl or heterocyclyl- $\text{C}_{2-6}$ -alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from  $-\text{CHF}_2$ ,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ ,  $-\text{OCHF}_2$ ,  $-\text{OCH}_2\text{CF}_3$ ,  $-\text{OCF}_2\text{CHF}_2$ ,  $-\text{SCF}_3$ ,  $-\text{OR}^{36}$ ,  $-\text{NR}^{36}\text{R}^{37}$ ,  $-\text{SR}^{36}$ ,  $-\text{S(O)}\text{R}^{36}$ ,  $-\text{S(O)}_2\text{R}^{36}$ ,  $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$ ,  
 5  $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$ ,  $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{C(O)}\text{R}^{36}$  and  $-\text{C(O)}\text{OR}^{36}$ ,

$\text{C}_{1-6}$ -alkyl,  $\text{C}_{2-6}$ -alkenyl and  $\text{C}_{2-6}$ -alkynyl,

which may optionally be substituted with one or more substituents selected from  $-\text{CHF}_2$ ,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ ,  $-\text{OCHF}_2$ ,  $-\text{OCH}_2\text{CF}_3$ ,  $-\text{OCF}_2\text{CHF}_2$ ,  
 10  $-\text{SCF}_3$ ,  $-\text{OR}^{36}$ ,  $-\text{NR}^{36}\text{R}^{37}$ ,  $-\text{SR}^{36}$ ,  $-\text{S(O)}\text{R}^{36}$ ,  $-\text{S(O)}_2\text{R}^{36}$ ,  $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$ ,  
 $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$ ,  $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{C(O)}\text{R}^{36}$  and  
 $-\text{C(O)}\text{OR}^{36}$ ,

15 aryl, aryloxy, aroyl, aryl- $\text{C}_{1-6}$ -alkoxy, aryl- $\text{C}_{1-6}$ -alkyl, aryl- $\text{C}_{2-6}$ -alkenyl, aryl- $\text{C}_{2-6}$ -alkynyl, heteroaryl, heteroaryl- $\text{C}_{1-6}$ -alkyl, heteroaryl- $\text{C}_{2-6}$ -alkenyl or heteroaryl- $\text{C}_{2-6}$ -alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from halogen,  $-\text{CN}$ ,  $-\text{CH}_2\text{CN}$ ,  $-\text{CHF}_2$ ,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ ,  
 20  $-\text{OCHF}_2$ ,  $-\text{OCH}_2\text{CF}_3$ ,  $-\text{OCF}_2\text{CHF}_2$ ,  $-\text{OS(O)}_2\text{CF}_3$ ,  $-\text{SCF}_3$ ,  $-\text{NO}_2$ ,  $-\text{OR}^{36}$ ,  $-\text{NR}^{36}\text{R}^{37}$ ,  
 $-\text{SR}^{36}$ ,  $-\text{NR}^{36}\text{S(O)}_2\text{R}^{37}$ ,  $-\text{S(O)}_2\text{NR}^{36}\text{R}^{37}$ ,  $-\text{S(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{S(O)}\text{R}^{36}$ ,  $-\text{S(O)}_2\text{R}^{36}$ ,  
 $-\text{OS(O)}_2\text{R}^{36}$ ,  $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$ ,  $-\text{CH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$ ,  
 $-\text{CH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{CH}_2\text{OR}^{36}$ ,  $-\text{CH}_2\text{NR}^{36}\text{R}^{37}$ ,  $-\text{OC(O)}\text{R}^{36}$ ,  $-\text{C(O)}\text{R}^{36}$  and  $-\text{C(O)}\text{OR}^{36}$ ,

25  $\text{C}_{1-6}$ -alkyl,  $\text{C}_{2-6}$ -alkenyl and  $\text{C}_{2-6}$ -alkynyl,

which may optionally be substituted with one or more substituents selected from  $-\text{CHF}_2$ ,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ ,  $-\text{OCHF}_2$ ,  $-\text{OCH}_2\text{CF}_3$ ,  $-\text{OCF}_2\text{CHF}_2$ ,  
 30  $-\text{SCF}_3$ ,  $-\text{OR}^{36}$ ,  $-\text{NR}^{36}\text{R}^{37}$ ,  $-\text{SR}^{36}$ ,  $-\text{S(O)}\text{R}^{36}$ ,  $-\text{S(O)}_2\text{R}^{36}$ ,  $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$ ,  
 $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$ ,  $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{C(O)}\text{R}^{36}$  and  
 $-\text{C(O)}\text{OR}^{36}$ ,

wherein  $\text{R}^{36}$  and  $\text{R}^{37}$  independently are hydrogen,  $\text{C}_{1-6}$ -alkyl or aryl,

of which the aryl moiety optionally may be substituted with one or more substituents selected from halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>38</sup>, -NR<sup>38</sup>R<sup>39</sup> and C<sub>1-6</sub>-alkyl,

5 wherein R<sup>38</sup> and R<sup>39</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl,

or R<sup>38</sup> and R<sup>37</sup> when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two  
10 double bonds,

or R<sup>23</sup> and R<sup>24</sup> when attached to the same ring carbon atom or different ring carbon atoms together may form a radical -O-(CH<sub>2</sub>)<sub>l</sub>-CR<sup>40</sup>R<sup>41</sup>-(CH<sub>2</sub>)<sub>l</sub>-O-, -(CH<sub>2</sub>)<sub>l</sub>-CR<sup>40</sup>R<sup>41</sup>-(CH<sub>2</sub>)<sub>l</sub>- or  
-S-(CH<sub>2</sub>)<sub>l</sub>-CR<sup>40</sup>R<sup>41</sup>-(CH<sub>2</sub>)<sub>l</sub>-S-,

15

wherein

t and l independently are 0, 1, 2, 3, 4 or 5,

20 R<sup>40</sup> and R<sup>41</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl,

R<sup>25</sup> to R<sup>30</sup> independently are hydrogen, halogen, -CN, -CF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>42</sup>, -NR<sup>42</sup>R<sup>43</sup>, C<sub>1-6</sub>-alkyl or C<sub>3-8</sub>-cycloalkyl,

25 wherein R<sup>42</sup> and R<sup>43</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl,

R<sup>31</sup>, R<sup>32</sup> and R<sup>33</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl,

R<sup>34</sup> and R<sup>35</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy, C<sub>1-6</sub>-alkanoyl, -C(O)NR<sup>44</sup>R<sup>45</sup>  
30 or -S(O)<sub>2</sub>R<sup>45</sup>,

aryl, aroyl, aryl-C<sub>1-6</sub>-alkoxy, aryl-C<sub>1-6</sub>-alkanoyl or aryl-C<sub>1-6</sub>-alkyl,

35

of which the aryl moieties optionally may be substituted with one or more substituents selected from halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OR<sup>44</sup>, -NR<sup>44</sup>R<sup>45</sup> and C<sub>1-6</sub>-alkyl,



wherein  $R^{44}$  and  $R^{45}$  independently are hydrogen or  $C_{1-6}$ -alkyl,

or  $R^{34}$  and  $R^{35}$  when attached to the carbon atom together with the said carbon atom may  
5 form a 3 to 8 membered cyclic ring optionally containing one or two heteroatoms selected  
from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds,

or  $R^{34}$  and  $R^{35}$  when attached to the nitrogen atom together with the said nitrogen atom may  
10 form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroa-  
toms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double  
bonds;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of  
these or a pharmaceutically acceptable salt thereof;

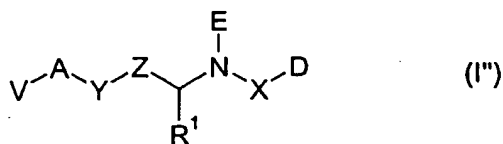
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having an  $IC_{50}$  value of no greater than  $5 \mu M$  as determined by the Glucagon Binding Assay  
(I), Glucagon Binding Assay (II) or Glucagon Binding Assay (III) disclosed herein.

By a compound of the general formula (I') having an  $IC_{50}$  value of no greater than  $5 \mu M$  as de-  
20 termined by the Glucagon Binding Assay (I), Glucagon Binding Assay (II) or Glucagon Binding  
Assay (III) is meant any compound of the defined formula having such activity, without limitation  
to any utility or usefulness for treating any specific indication.

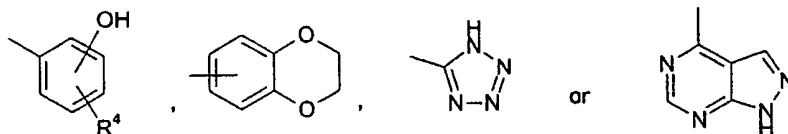
In a further aspect the invention relates to compounds of the general formula (I''):

25



wherein

V is  $-\text{C}(\text{O})\text{OR}^2$ ,  $-\text{C}(\text{O})\text{NR}^2\text{R}^3$ ,  $-\text{C}(\text{O})\text{NR}^2\text{OR}^3$ ,  $-\text{S}(\text{O})_2\text{OR}^2$ ,



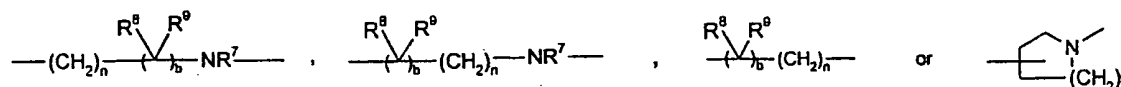
wherein

$\text{R}^2$  and  $\text{R}^3$  independently are hydrogen or  $\text{C}_{1-6}$ -alkyl,

$\text{R}^4$  is hydrogen, halogen,  $-\text{CN}$ ,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ ,  $-\text{NO}_2$ ,  $-\text{OR}^5$ ,  $-\text{NR}^5\text{R}^6$  or  $\text{C}_{1-6}$ -alkyl,

wherein  $\text{R}^5$  and  $\text{R}^6$  independently are hydrogen or  $\text{C}_{1-6}$ -alkyl,

A is



wherein

b is 0 or 1,

n is 0, 1, 2 or 3,

$\text{R}^7$  is hydrogen,  $\text{C}_{1-6}$ -alkyl or  $\text{C}_{3-8}$ -cycloalkyl- $\text{C}_{1-6}$ -alkyl,

$\text{R}^8$  and  $\text{R}^9$  independently are hydrogen or  $\text{C}_{1-6}$ -alkyl,

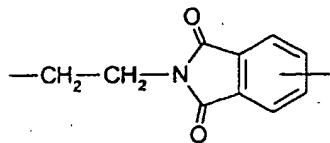
Y is  $-\text{C}(\text{O})-$ ,  $-\text{S}(\text{O})_2-$ ,  $-\text{O}-$  or a valence bond,

Z is phenylene or a divalent radical derived from a 5 or 6 membered heteroaromatic ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur,

which may optionally be attached to one or two groups  $\text{R}^{46}$  and  $\text{R}^{47}$  selected from hydrogen, halogen,  $-\text{CN}$ ,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ ,  $-\text{NO}_2$ ,  $-\text{OR}^{10}$ ,  $-\text{NR}^{10}\text{R}^{11}$  and  $\text{C}_{1-6}$ -alkyl,

wherein  $R^{10}$  and  $R^{11}$  independently are hydrogen or  $C_{1-6}$ -alkyl,

or -A-Y-Z- together are



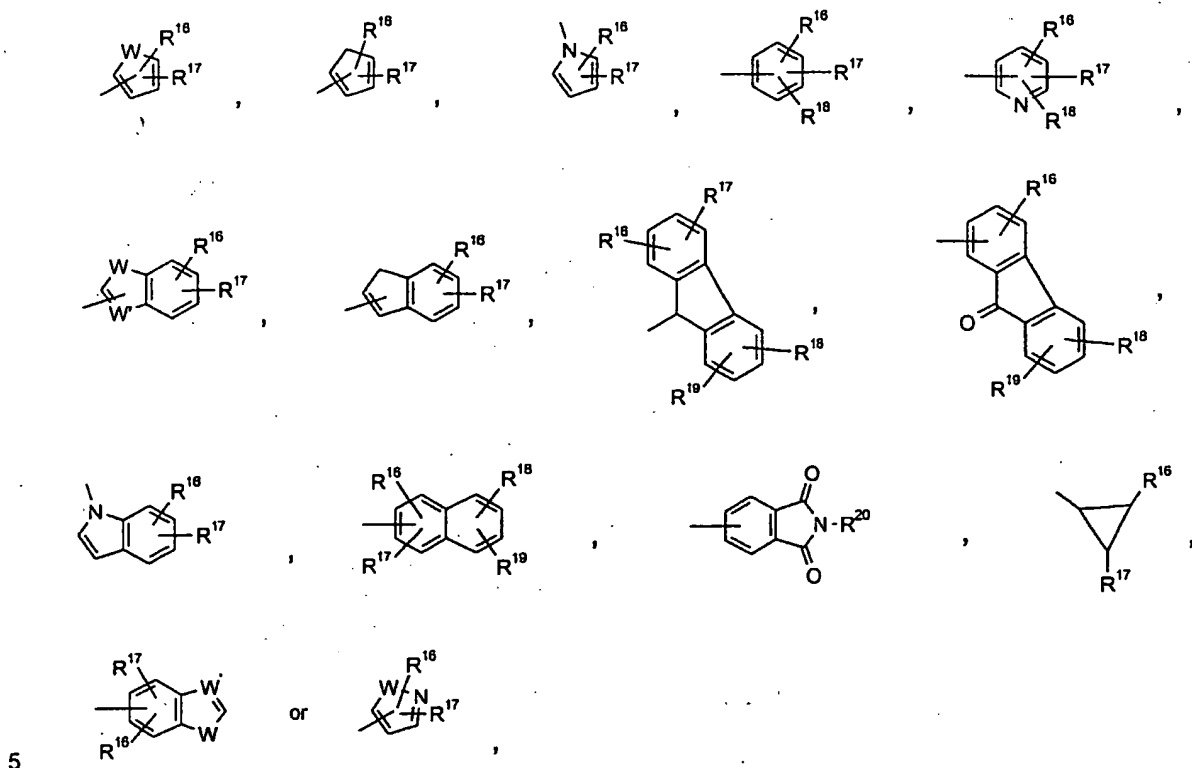
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$R^1$  is hydrogen or  $C_{1-6}$ -alkyl,



**R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup> and R<sup>15</sup> independently are hydrogen or C<sub>1-8</sub>-alkyl,**

D is



wherein

W is -O-, -S-, -S(O)<sub>2</sub>- or -NR<sup>20</sup>-,

$W'$  is  $=CR^{20'}$  - or  $=N-$ ,

$R^{20}$  and  $R^{20'}$  are hydrogen,  $C_{1-6}$ -alkyl or  $C_{3-6}$ -cycloalkyl- $C_{1-6}$ -alkyl,

15.  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$  and  $R^{19}$  independently are

- hydrogen, halogen, -CN, -CH<sub>2</sub>CN, -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -OS(O)<sub>2</sub>CF<sub>3</sub>, -SCF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>, -SR<sup>21</sup>, -NR<sup>21</sup>S(O)<sub>2</sub>R<sup>22</sup>, -S(O)<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>, -S(O)NR<sup>21</sup>R<sup>22</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -OS(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, -OC(O)NR<sup>21</sup>R<sup>22</sup>,

-NR<sup>21</sup>C(O)R<sup>22</sup>, -CH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -CH<sub>2</sub>OR<sup>21</sup>, -CH<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>,  
-OC(O)R<sup>21</sup>, -C(O)R<sup>21</sup> or -C(O)OR<sup>21</sup>,

- C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl or C<sub>2-6</sub>-alkynyl,

which may optionally be substituted with one or more substituents selected from

-CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -SCF<sub>3</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>,  
-SR<sup>21</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, -OC(O)NR<sup>21</sup>R<sup>22</sup>, -NR<sup>21</sup>C(O)R<sup>22</sup>,  
-OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -C(O)R<sup>21</sup> and -C(O)OR<sup>21</sup>,

- C<sub>3-8</sub>-cycloalkyl, C<sub>3-8</sub>-cycloalkenyl, heterocyclyl, C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkyl, C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkoxy, C<sub>3-8</sub>-cycloalkyloxy, C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkylthio, C<sub>3-8</sub>-cycloalkylthio, C<sub>3-8</sub>-cycloalkyl-C<sub>2-6</sub>-alkenyl, C<sub>3-8</sub>-cycloalkyl-C<sub>2-6</sub>-alkynyl, C<sub>3-8</sub>-cycloalkenyl-C<sub>1-6</sub>-alkyl, C<sub>3-8</sub>-cycloalkenyl-C<sub>2-6</sub>-alkenyl, C<sub>3-8</sub>-cycloalkenyl-C<sub>2-6</sub>-alkynyl, heterocyclyl-C<sub>1-6</sub>-alkyl, heterocyclyl-C<sub>2-6</sub>-alkenyl or heterocyclyl-C<sub>2-6</sub>-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from

-CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -SCF<sub>3</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>,  
-SR<sup>21</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, -OC(O)NR<sup>21</sup>R<sup>22</sup>, -NR<sup>21</sup>C(O)R<sup>22</sup>,  
-OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -C(O)R<sup>21</sup> and -C(O)OR<sup>21</sup>,

- C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl and C<sub>2-6</sub>-alkynyl,

which may optionally be substituted with one or more substituents selected from

-CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -SCF<sub>3</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>, -SR<sup>21</sup>,  
-S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, -OC(O)NR<sup>21</sup>R<sup>22</sup>, -NR<sup>21</sup>C(O)R<sup>22</sup>, -OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>,  
-C(O)R<sup>21</sup> and -C(O)OR<sup>21</sup>,

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C<sub>1-6</sub>-alkoxy, aryl-C<sub>1-6</sub>-alkyl, aryl-C<sub>2-6</sub>-alkenyl, aryl-C<sub>2-6</sub>-alkynyl, heteroaryl, heteroaryl-C<sub>1-6</sub>-alkyl, heteroaryl-C<sub>2-6</sub>-alkenyl or heteroaryl-C<sub>2-6</sub>-alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from

halogen, -CN, -CH<sub>2</sub>CN, -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>,  
 5 -OS(O)<sub>2</sub>CF<sub>3</sub>, -SCF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>, -SR<sup>21</sup>, -NR<sup>21</sup>S(O)<sub>2</sub>R<sup>22</sup>, -S(O)<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>,  
 -S(O)NR<sup>21</sup>R<sup>22</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -OS(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, -OC(O)NR<sup>21</sup>R<sup>22</sup>,  
 -NR<sup>21</sup>C(O)R<sup>22</sup>, -CH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -CH<sub>2</sub>OR<sup>21</sup>, -CH<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>,  
 -OC(O)R<sup>21</sup>, -C(O)R<sup>21</sup> and -C(O)OR<sup>21</sup>,

10 C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl and C<sub>2-6</sub>-alkynyl,

which may optionally be substituted with one or more substituents selected from -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>,  
 -SCF<sub>3</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>, -SR<sup>21</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>,  
 15 -OC(O)NR<sup>21</sup>R<sup>22</sup>, -NR<sup>21</sup>C(O)R<sup>22</sup>, -OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -C(O)R<sup>21</sup> and  
 -C(O)OR<sup>21</sup>,

wherein R<sup>21</sup> and R<sup>22</sup> independently are hydrogen, -CF<sub>3</sub>, C<sub>1-6</sub>-alkyl, tri-C<sub>1-6</sub>-alkylsilyl, C<sub>3-6</sub>-cyclo-  
 alkyl, C<sub>3-6</sub>-cycloalkyl-C<sub>1-6</sub>-alkyl, aryl, aryl-C<sub>1-6</sub>-alkyl or heteroaryl, or R<sup>21</sup> and R<sup>22</sup> when at-  
 20 tached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8  
 membered heterocyclic ring optionally containing one or two further heteroatoms selected  
 from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R<sup>16</sup> to R<sup>19</sup> when placed in adjacent positions together may form a bridge  
 25 -(CR<sup>16</sup>R<sup>17</sup>)<sub>a</sub>-O-(CR<sup>18</sup>R<sup>19</sup>)<sub>c</sub>-O-,

wherein

a is 0, 1 or 2,

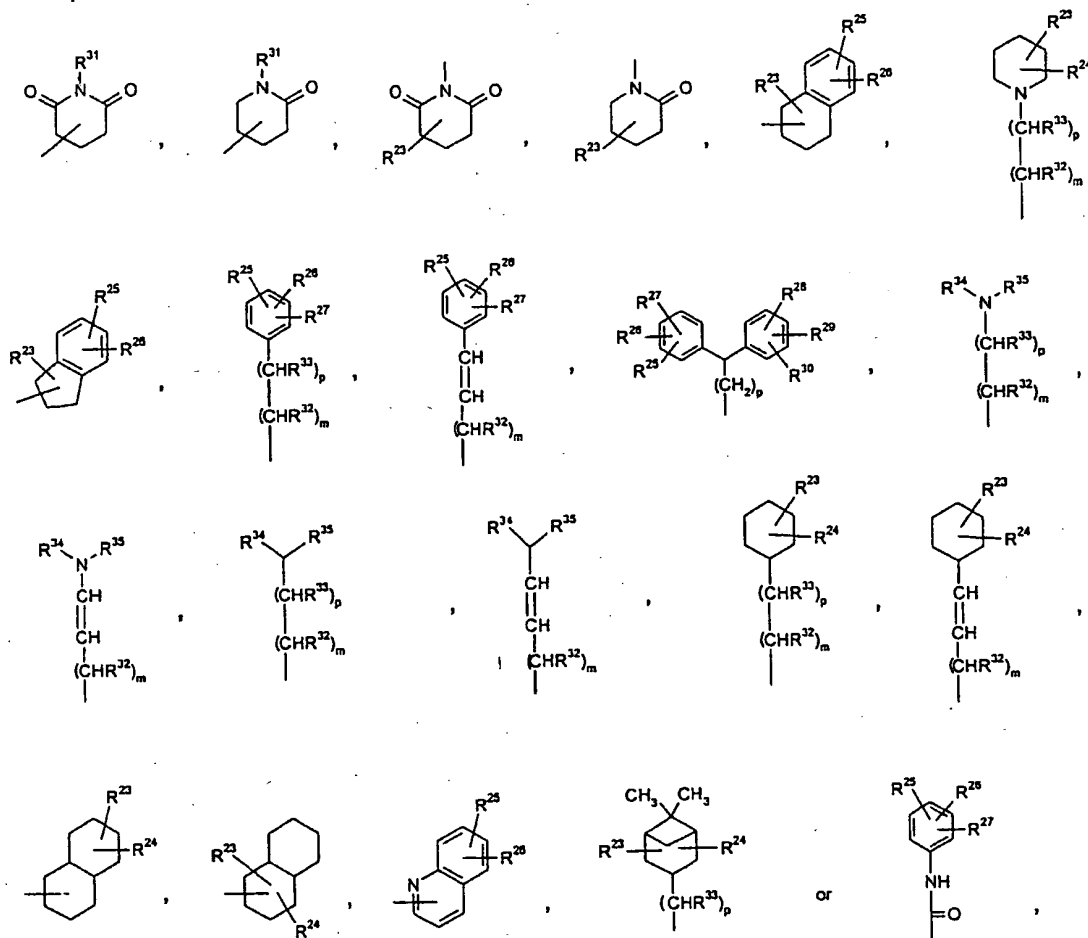
c is 1 or 2,

R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup> and R<sup>19</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl or halogen,

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E is a 3 to 9 membered mono- or bicyclic ring which may optionally contain one or two double bonds and which may optionally contain one or two heteroatoms selected from nitrogen, oxygen and sulfur, wherein one or two groups R<sup>23</sup> and R<sup>24</sup> may be attached to the same or different ring carbon atoms and wherein a group R<sup>31</sup> may be attached to a ring nitrogen atom

5 when present, or



wherein

10 m and p independently are 0, 1, 2, 3 or 4, with the proviso that when both m and p are present in the same formula at least one of m and p is different from 0,

$R^{23}$  and  $R^{24}$  independently are



- hydrogen,  $-\text{CHF}_2$ ,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ ,  $-\text{OCHF}_2$ ,  $-\text{OCH}_2\text{CF}_3$ ,  $-\text{OCF}_2\text{CHF}_2$ ,  $-\text{SCF}_3$ ,  $-\text{OR}^{36}$ ,  $-\text{NR}^{36}\text{R}^{37}$ ,  $-\text{SR}^{36}$ ,  $-\text{S(O)}\text{R}^{36}$ ,  $-\text{S(O)}_2\text{R}^{36}$ ,  $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$ ,  $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{C(O)}\text{R}^{36}$  or  $-\text{C(O)}\text{OR}^{36}$ ,

- 5 •  $\text{C}_{1-6}$ -alkyl,  $\text{C}_{2-6}$ -alkenyl or  $\text{C}_{2-6}$ -alkynyl,

which may optionally be substituted with one or more substituents selected from

- 10  $-\text{CHF}_2$ ,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ ,  $-\text{OCHF}_2$ ,  $-\text{OCH}_2\text{CF}_3$ ,  $-\text{OCF}_2\text{CHF}_2$ ,  $-\text{SCF}_3$ ,  $-\text{OR}^{36}$ ,  $-\text{NR}^{36}\text{R}^{37}$ ,  $-\text{SR}^{36}$ ,  $-\text{S(O)}\text{R}^{36}$ ,  $-\text{S(O)}_2\text{R}^{36}$ ,  $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$ ,  $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{C(O)}\text{R}^{36}$  and  $-\text{C(O)}\text{OR}^{36}$ ,

- 15 •  $\text{C}_{3-8}$ -cycloalkyl,  $\text{C}_{3-8}$ -cycloalkylidene,  $\text{C}_{3-8}$ -cycloalkenyl, heterocyclyl,  $\text{C}_{3-8}$ -cycloalkyl- $\text{C}_{1-6}$ -alkyl,  $\text{C}_{3-8}$ -cycloalkyl- $\text{C}_{2-6}$ -alkenyl,  $\text{C}_{3-8}$ -cycloalkyl- $\text{C}_{2-6}$ -alkynyl,  $\text{C}_{3-8}$ -cycloalkenyl- $\text{C}_{1-6}$ -alkyl,  $\text{C}_{3-8}$ -cycloalkenyl- $\text{C}_{2-6}$ -alkenyl,  $\text{C}_{3-8}$ -cycloalkenyl- $\text{C}_{2-6}$ -alkynyl, heterocyclyl- $\text{C}_{1-6}$ -alkyl, heterocyclyl- $\text{C}_{2-6}$ -alkenyl or heterocyclyl- $\text{C}_{2-6}$ -alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from

- 20  $-\text{CHF}_2$ ,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ ,  $-\text{OCHF}_2$ ,  $-\text{OCH}_2\text{CF}_3$ ,  $-\text{OCF}_2\text{CHF}_2$ ,  $-\text{SCF}_3$ ,  $-\text{OR}^{36}$ ,  $-\text{NR}^{36}\text{R}^{37}$ ,  $-\text{SR}^{36}$ ,  $-\text{S(O)}\text{R}^{36}$ ,  $-\text{S(O)}_2\text{R}^{36}$ ,  $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$ ,  $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{C(O)}\text{R}^{36}$  and  $-\text{C(O)}\text{OR}^{36}$ ,

$\text{C}_{1-6}$ -alkyl,  $\text{C}_{2-6}$ -alkenyl and  $\text{C}_{2-6}$ -alkynyl,

25

which may optionally be substituted with one or more substituents selected from  $-\text{CHF}_2$ ,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ ,  $-\text{OCHF}_2$ ,  $-\text{OCH}_2\text{CF}_3$ ,  $-\text{OCF}_2\text{CHF}_2$ ,  $-\text{SCF}_3$ ,  $-\text{OR}^{36}$ ,  $-\text{NR}^{36}\text{R}^{37}$ ,  $-\text{SR}^{36}$ ,  $-\text{S(O)}\text{R}^{36}$ ,  $-\text{S(O)}_2\text{R}^{36}$ ,  $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$ ,  $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$ ,  $-\text{C(O)}\text{R}^{36}$  and  $-\text{C(O)}\text{OR}^{36}$ ,

30

- aryl, aryloxy, aroyl, aryl- $\text{C}_{1-6}$ -alkoxy, aryl- $\text{C}_{1-6}$ -alkyl, aryl- $\text{C}_{2-6}$ -alkenyl, aryl- $\text{C}_{2-6}$ -alkynyl, heteroaryl, heteroaryl- $\text{C}_{1-6}$ -alkyl, heteroaryl- $\text{C}_{2-6}$ -alkenyl or heteroaryl- $\text{C}_{2-6}$ -alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from

halogen, -CN, -CH<sub>2</sub>CN, -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>,  
 -OS(O)<sub>2</sub>CF<sub>3</sub>, -SCF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>36</sup>, -NR<sup>36</sup>R<sup>37</sup>, -SR<sup>36</sup>, -NR<sup>36</sup>S(O)<sub>2</sub>R<sup>37</sup>, -S(O)<sub>2</sub>NR<sup>36</sup>R<sup>37</sup>,  
 -S(O)NR<sup>36</sup>R<sup>37</sup>, -S(O)R<sup>36</sup>, -S(O)<sub>2</sub>R<sup>36</sup>, -OS(O)<sub>2</sub>R<sup>36</sup>, -C(O)NR<sup>36</sup>R<sup>37</sup>, -OC(O)NR<sup>36</sup>R<sup>37</sup>,  
 -NR<sup>36</sup>C(O)R<sup>37</sup>, -CH<sub>2</sub>C(O)NR<sup>36</sup>R<sup>37</sup>, -CH<sub>2</sub>C(O)NR<sup>36</sup>R<sup>37</sup>, -CH<sub>2</sub>OR<sup>36</sup>, -CH<sub>2</sub>NR<sup>36</sup>R<sup>37</sup>,  
 -OC(O)R<sup>36</sup>, -C(O)R<sup>36</sup> and -C(O)OR<sup>36</sup>,

C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl and C<sub>2-6</sub>-alkynyl,

which may optionally be substituted with one or more substituents selected from -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>,  
 -SCF<sub>3</sub>, -OR<sup>36</sup>, -NR<sup>36</sup>R<sup>37</sup>, -SR<sup>36</sup>, -S(O)R<sup>36</sup>, -S(O)<sub>2</sub>R<sup>36</sup>, -C(O)NR<sup>36</sup>R<sup>37</sup>,  
 -OC(O)NR<sup>36</sup>R<sup>37</sup>, -NR<sup>36</sup>C(O)R<sup>37</sup>, -OCH<sub>2</sub>C(O)NR<sup>36</sup>R<sup>37</sup>, -C(O)R<sup>36</sup> and  
 -C(O)OR<sup>36</sup>,

wherein R<sup>36</sup> and R<sup>37</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl or aryl,

of which the aryl moiety optionally may be substituted with one or more substituents selected from halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>38</sup>, -NR<sup>38</sup>R<sup>39</sup> and C<sub>1-6</sub>-alkyl,

wherein R<sup>38</sup> and R<sup>39</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl,

or R<sup>36</sup> and R<sup>37</sup> when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or R<sup>23</sup> and R<sup>24</sup> when attached to the same ring carbon atom or different ring carbon atoms together may form a radical -O-(CH<sub>2</sub>)<sub>t</sub>-CR<sup>40</sup>R<sup>41</sup>-(CH<sub>2</sub>)<sub>t</sub>-O-, -(CH<sub>2</sub>)<sub>t</sub>-CR<sup>40</sup>R<sup>41</sup>-(CH<sub>2</sub>)<sub>t</sub>- or -S-(CH<sub>2</sub>)<sub>t</sub>-CR<sup>40</sup>R<sup>41</sup>-(CH<sub>2</sub>)<sub>t</sub>-S-,

wherein

t and l independently are 0, 1, 2, 3, 4 or 5,

5 R<sup>40</sup> and R<sup>41</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl,

R<sup>25</sup> to R<sup>30</sup> independently are hydrogen, halogen, -CN, -CF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>42</sup>, -NR<sup>42</sup>R<sup>43</sup>, C<sub>1-6</sub>-alkyl, C<sub>3-8</sub>-cycloalkyl or C<sub>3-8</sub>-cycloalkenyl,

10 wherein R<sup>42</sup> and R<sup>43</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl, or

R<sup>42</sup> and R<sup>43</sup> when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two  
15 double bonds,

R<sup>31</sup>, R<sup>32</sup> and R<sup>33</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl,

R<sup>34</sup> and R<sup>35</sup> independently are  
20

- hydrogen, C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy, C<sub>1-6</sub>-alkanoyl, -C(O)NR<sup>44</sup>R<sup>45</sup> or -S(O)<sub>2</sub>R<sup>45</sup>,
- aryl, aroyl, aryl-C<sub>1-6</sub>-alkoxy, aryl-C<sub>1-6</sub>-alkanoyl or aryl-C<sub>1-6</sub>-alkyl,

25 of which the aryl moieties optionally may be substituted with one or more substituents selected from halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OR<sup>44</sup>, -NR<sup>44</sup>R<sup>45</sup> and C<sub>1-6</sub>-alkyl,

wherein R<sup>44</sup> and R<sup>45</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl, or

30 R<sup>34</sup> and R<sup>35</sup> when attached to the carbon atom together with the said carbon atom may form a 3 to 8 membered cyclic ring optionally containing one or two heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds, or

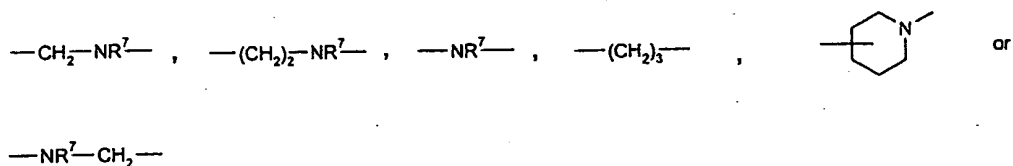
R<sup>34</sup> and R<sup>35</sup> when attached to the nitrogen atom together with the said nitrogen atom may  
35 form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroa-

toms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds,

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

In a preferred embodiment V is  $-C(O)OH$ ,  $-S(O)_2OH$ ,  $-C(O)NHOH$  or 5-tetrazolyl, and more preferred  $-C(O)OH$  or 5-tetrazolyl.

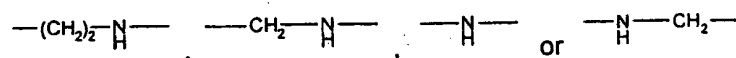
In a preferred embodiment A is



wherein  $R^7$  is as defined for formula (I).

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More preferred A is

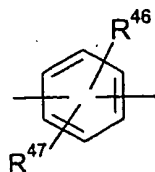


In a preferred embodiment Y is  $-C(O)-$ .

In another preferred embodiment Y is a valence bond.

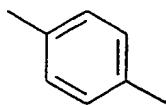
In a preferred embodiment Z is

25



wherein  $R^{46}$  and  $R^{47}$  are as defined for formula (I).

More preferably, Z is

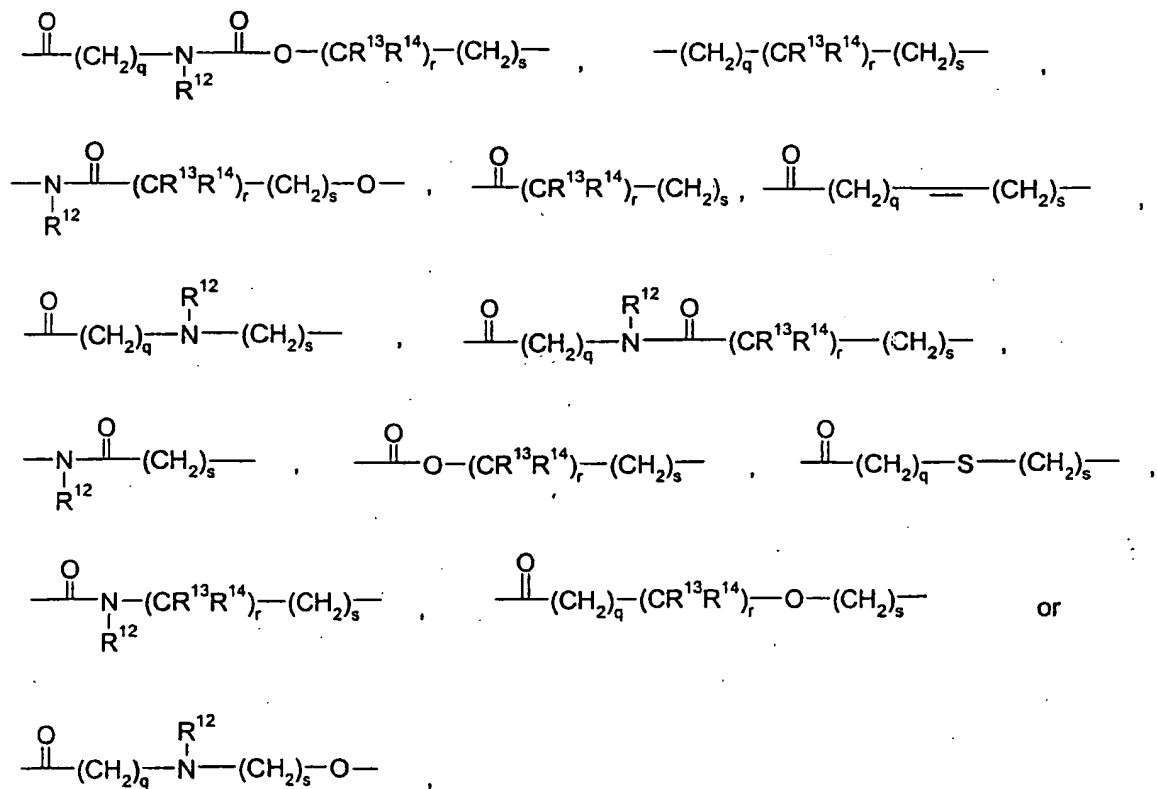


5 In a preferred embodiment  $R^1$  is hydrogen.

In another preferred embodiment  $R^1$  is methyl.

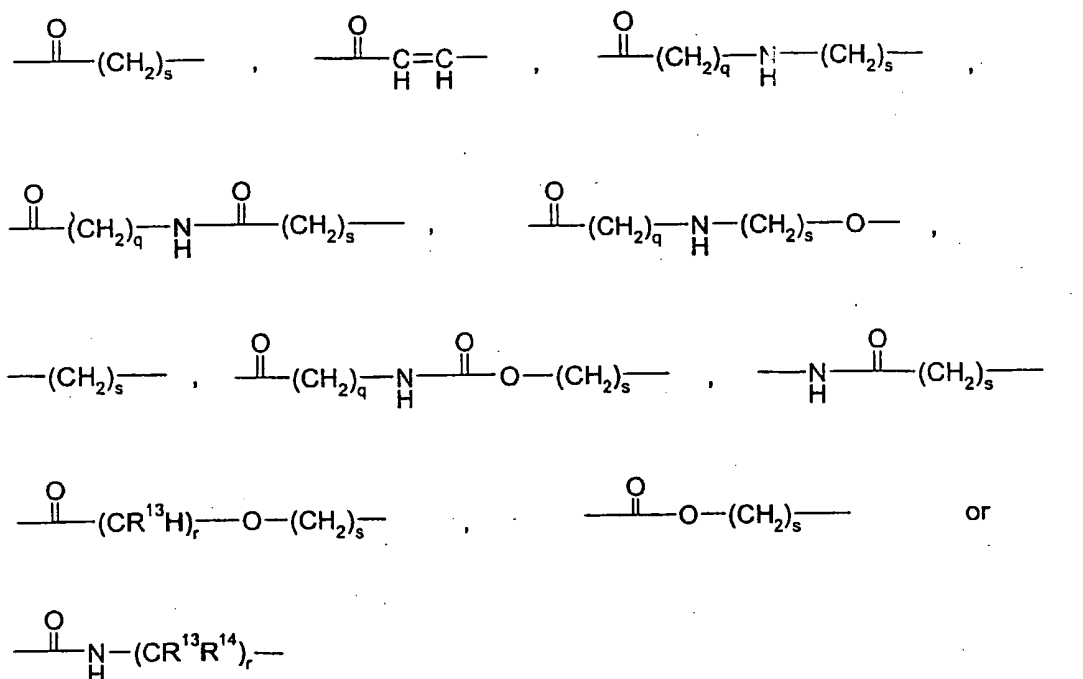
In a preferred embodiment X is

10



wherein q, r, s,  $R^{12}$ ,  $R^{13}$  and  $R^{14}$  are as defined for formula (I).

More preferably, X is



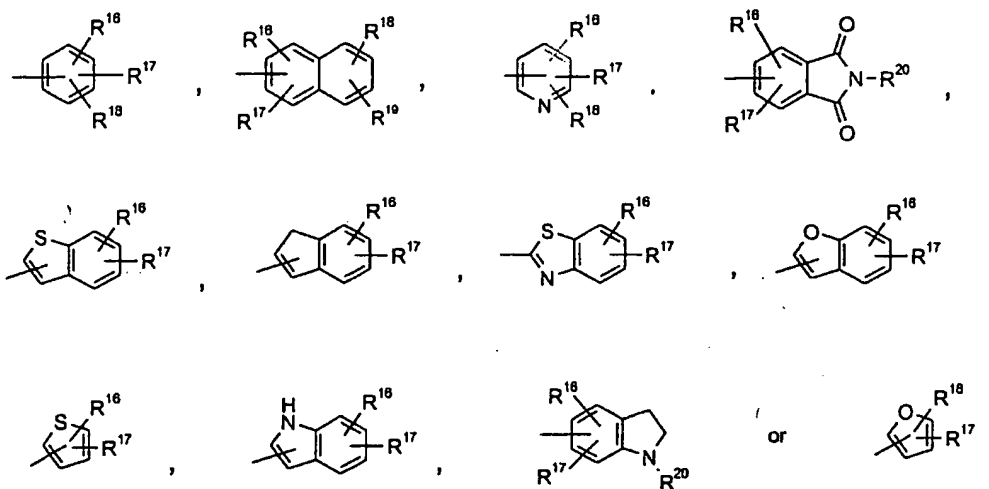
- 5 wherein q is 0 or 1, r is 0 or 1, s is 0, 1 or 2, and R<sup>13</sup> is hydrogen or C<sub>1-6</sub>-alkyl.

Even more preferably, X is -C(O)NH-, -C(O)NHCH<sub>2</sub>-, -C(O)NHCH(CH<sub>3</sub>)-, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>-, -C(O)CH<sub>2</sub>-, -C(O)CH=CH-, -(CH<sub>2</sub>)<sub>s</sub>-, -C(O)-, -C(O)O- or -NHC(O)-, wherein s is 0 or 1.

- 10 Still more preferably, X is -C(O)NH-, -C(O)NHCH<sub>2</sub>-, -C(O)NHCH(CH<sub>3</sub>)-, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>-, -C(O)CH<sub>2</sub>-, -(CH<sub>2</sub>)-, -C(O)- or -NHC(O)-.

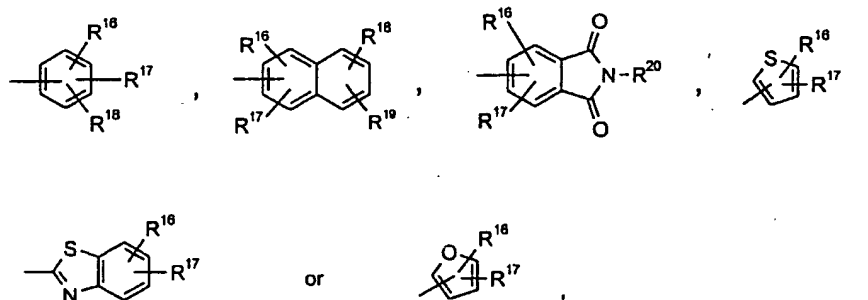
Of these X is preferably -C(O)NH- or -C(O)NHCH(CH<sub>3</sub>)-.

In a preferred embodiment D is



5 wherein  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$  and  $R^{20}$  are as defined for formula (I).

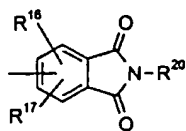
More preferably, D is



10

wherein  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$  and  $R^{20}$  are as defined for formula (I).

In a preferred embodiment D is



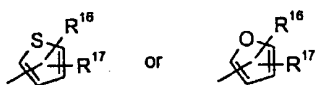
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wherein  $R^{16}$ ,  $R^{17}$  and  $R^{20}$  are as defined for formula (I).

More preferably,  $R^{16}$  and  $R^{17}$  are both hydrogen and  $R^{20}$  is  $C_{1-6}$ -alkyl or  $C_{3-8}$ -cycloalkyl- $C_{1-6}$ -alkyl. Even more preferably,  $R^{20}$  is cyclopropylmethyl, butyl or isopropyl, especially preferred isopropyl.

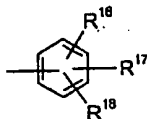
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In another preferred embodiment D is



10 wherein  $R^{16}$  and  $R^{17}$  are as defined for formula (I).

In yet another preferred embodiment D is



15

wherein  $R^{16}$ ,  $R^{17}$  and  $R^{18}$  are as defined for formula (I).

Preferably,  $R^{16}$ ,  $R^{17}$  and  $R^{18}$  are independently

20 hydrogen, halogen, -CN, -NO<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, hydroxy, -SCF<sub>3</sub>,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkyl substituted with hydroxy,  $C_{1-6}$ -alkyl substituted with -S(O)<sub>2</sub>R<sup>21</sup>,  $C_{1-6}$ -alkoxy, -S- $C_{1-6}$ -alkyl, -C(O)OR<sup>21</sup>, -C(O)R<sup>21</sup>, -CH<sub>2</sub>(O)R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -S(O)<sub>2</sub>CF<sub>3</sub>, -S(O)<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>,  $C_{3-8}$ -cycloalkyl,  $C_{3-8}$ -cycloalkyl- $C_{1-6}$ -alkoxy,  $C_{3-8}$ -cycloalkyl- $C_{1-6}$ -alkylthio or  $C_{3-8}$ -cycloalkylthio,

25 wherein R<sup>21</sup> and R<sup>22</sup> independently are hydrogen,  $C_{1-6}$ -alkyl, tri- $C_{1-6}$ -alkylsilyl,  $C_{3-8}$ -cycloalkyl,  $C_{3-8}$ -cycloalkyl- $C_{1-6}$ -alkyl, phenyl, phenyl- $C_{1-6}$ -alkyl, 2,3-dihydroindolyl or isoindolyl, or R<sup>21</sup> and R<sup>22</sup> together with the nitrogen atom to which they are attached form a piperidine ring,

30 phenoxy, phenoxycarbonyl, phenyl, phenyl- $C_{1-6}$ -alkoxy, phenyl- $C_{1-6}$ -alkyl, furanyl, tetrazolyl, benzoxazolyl or oxadiazolyl, of which the ring systems optionally may be substituted with halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -NO<sub>2</sub>, -C(O)OR<sup>21</sup>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup> or  $C_{1-6}$ -alkyl, wherein R<sup>21</sup> and R<sup>22</sup> independently are hydrogen or  $C_{1-6}$ -alkyl, or



wherein  $R^{16}$  and  $R^{17}$  in adjacent positions form the radical  $-O-CH_2-O-$ ,  $-CF_2-O-CF_2-O-$  or  $-O-CF_2-CF_2-O-$ , and  $R^{18}$  is hydrogen.

5 More preferably,  $R^{16}$ ,  $R^{17}$  and  $R^{18}$  are independently

hydrogen, halogen,  $-CN$ ,  $-NO_2$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-SCF_3$ ,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkyl substituted with hydroxy,  $C_{1-6}$ -alkyl substituted with  $-S(O)_2R^{21}$ ,  $C_{1-6}$ -alkoxy,  $-S-C_{1-6}$ -alkyl,  $-C(O)OR^{21}$ ,  $-C(O)R^{21}$ ,  $-CH_2(O)R^{21}$ ,  $-C(O)NR^{21}R^{22}$ ,  $-S(O)R^{21}$ ,  $-S(O)_2R^{21}$ ,  $-S(O)_2CF_3$ ,  $-S(O)_2NR^{21}R^{22}$ ,  $C_{3-8}$ -cyclo-  
10 alkyl- $C_{1-6}$ -alkoxy,  $C_{3-8}$ -cycloalkyl- $C_{1-6}$ -alkylthio or  $C_{3-8}$ -cycloalkylthio,

wherein  $R^{21}$  and  $R^{22}$  independently are hydrogen,  $C_{1-6}$ -alkyl, tri- $C_{1-6}$ -alkylsilyl,  $C_{3-8}$ -cycloalkyl,  $C_{3-8}$ -cycloalkyl- $C_{1-6}$ -alkyl, phenyl or 2,3-dihydroindolyl, or  $R^{21}$  and  $R^{22}$  together with the nitrogen atom to which they are attached form a piperidine ring,

15

phenoxy, phenyl, benzyl, furanyl, tetrazolyl, benzoxazolyl or oxadiazolyl, of which the ring systems optionally may be substituted with halogen,  $-C(O)OR^{21}$  or  $C_{1-6}$ -alkyl, wherein  $R^{21}$  is hydrogen or  $C_{1-6}$ -alkyl, or

20 wherein  $R^{16}$  and  $R^{17}$  in adjacent positions form the radical  $-CF_2-O-CF_2-O-$  or  $-O-CF_2-CF_2-O-$ , and  $R^{18}$  is hydrogen.

Even more preferably,  $R^{16}$ ,  $R^{17}$  and  $R^{18}$  independently are

25 hydrogen, halogen,  $-CN$ ,  $-NO_2$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-SCF_3$ ,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkyl substituted with hydroxy,  $C_{1-6}$ -alkoxy,  $-S-C_{1-6}$ -alkyl,  $-C(O)OR^{21}$ ,  $-C(O)R^{21}$ ,  $-CH_2(O)R^{21}$ ,  $-C(O)NR^{21}R^{22}$ ,  $-S(O)_2R^{21}$ ,  $-(O)_2CF_3$  or  $-S(O)_2NR^{21}R^{22}$ ,

wherein  $R^{21}$  and  $R^{22}$  independently are hydrogen,  $C_{1-6}$ -alkyl, tri- $C_{1-6}$ -alkylsilyl, phenyl or  
30 2,3-dihydroindolyl,

phenoxy, phenyl, benzyl, furanyl, tetrazolyl, benzoxazolyl or oxadiazolyl, of which the ring systems optionally may be substituted with halogen,  $-C(O)OR^{21}$  or  $C_{1-6}$ -alkyl, wherein  $R^{21}$  is hydrogen or  $C_{1-6}$ -alkyl, or

35

wherein  $R^{16}$  and  $R^{17}$  in adjacent positions form the radical  $-CF_2-O-CF_2-O-$  or  $-O-CF_2-CF_2-O-$ , and  $R^{18}$  is hydrogen.

Still more preferably,  $R^{16}$ ,  $R^{17}$  and  $R^{18}$  are independently hydrogen, halogen,  $-CN$ ,  $-NO_2$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-SCF_3$ ,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy,  $-S-C_{1-6}$ -alkyl,  $-C(O)OC_{1-6}$ -alkyl,  $-S(O)_2C_{1-6}$ -alkyl,  $-S(O)_2CF_3$ ,  $-C(O)N(C_{1-6}$ -alkyl)( $C_{1-6}$ -alkyl),  $-S(O)_2N(phenyl)(C_{1-6}$ -alkyl),  $-C(=O)C_{1-6}$ -alkyl,  $-CH_2OH$ ,  $-CH_2O(tri-C_{1-6}$ -alkylsilyl), 2,3-dihydroindol-1-ylsulfonyl, phenoxy, phenyl, 4-chlorophenyl, 1,3,5-trimethylbenzyl, benzoxazolyl, 2-methyltetrazol-5-yl, 2-methyl-3-methoxycarbonylfuran-5-yl or 3-isopropyl-[1,2,4]oxadiazol-5-yl).

10

In a preferred embodiment one of  $R^{16}$  to  $R^{18}$  is hydrogen.

In another preferred embodiment two of  $R^{16}$  to  $R^{18}$  are hydrogen.

15 In yet another preferred embodiment  $R^{16}$  and  $R^{17}$  are both hydrogen and  $R^{18}$  is  $-OCF_3$ ,  $-SCF_3$ ,  $-CF_3$ ,  $-S(O)_2CH_3$ , phenyl, halogen,  $C_{1-6}$ -alkyl, nitro,  $-S-C_{1-6}$ -alkyl or  $-S(O)_2NR^{21}R^{22}$ , wherein  $R^{21}$  is  $C_{1-6}$ -alkyl and  $R^{22}$  is phenyl.

20 In still another preferred embodiment  $R^{16}$  and  $R^{17}$  are both hydrogen and  $R^{18}$  is  $-OCF_3$  or halogen.

In a further embodiment  $R^{16}$  is hydrogen and  $R^{17}$  and  $R^{18}$  are both halogen or are both  $-CF_3$ .

25 In yet a further embodiment  $R^{16}$  is hydrogen,  $R^{17}$  is  $-CF_3$  and  $R^{18}$  is halogen,  $-CN$ ,  $C_{1-6}$ -alkoxy or  $-OCF_3$ .

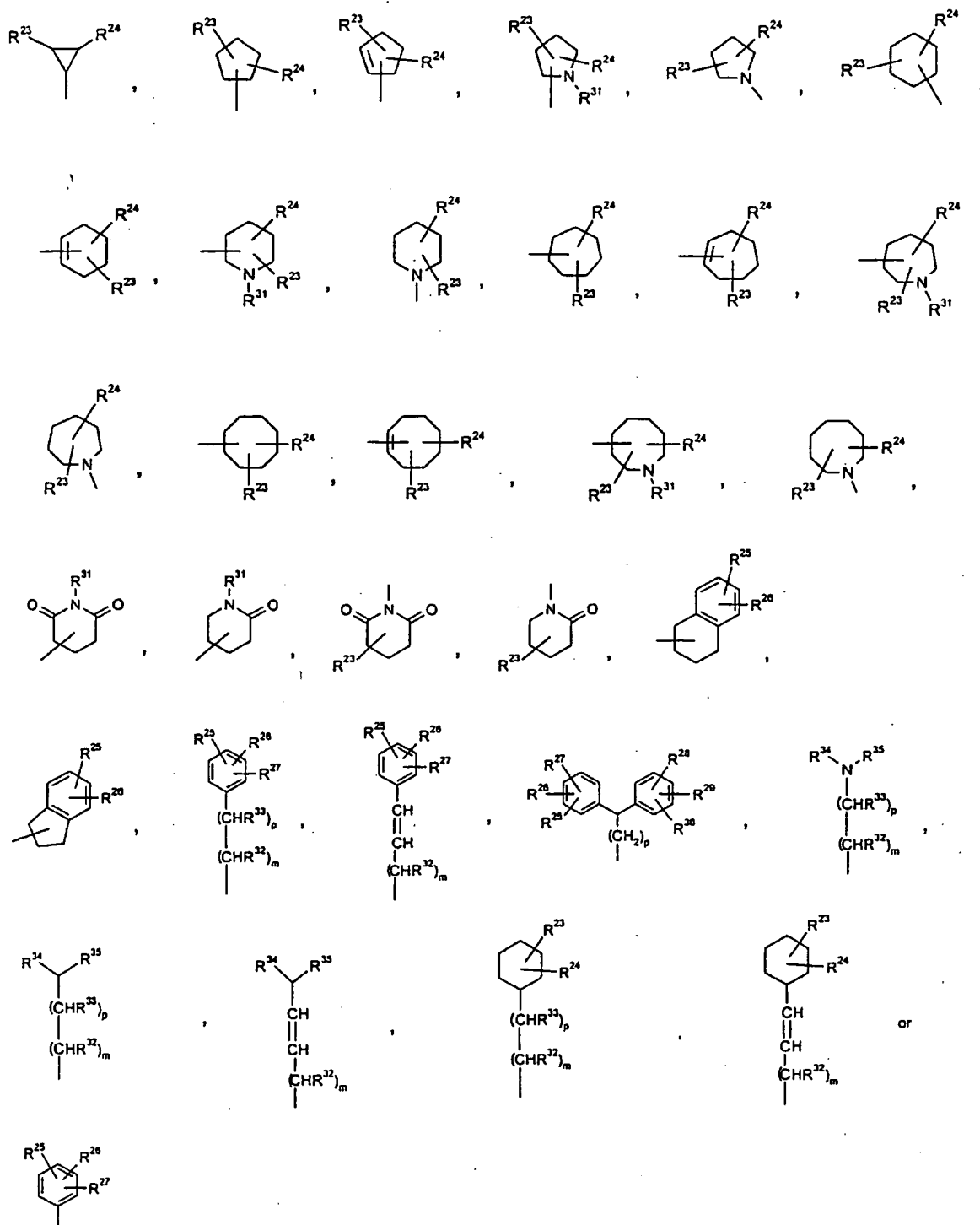
In still a further embodiment  $R^{16}$  is hydrogen,  $R^{17}$  is  $-OCF_3$  and  $R^{18}$  is  $-S(O)_2CH_3$ ,  $-CH_2O-tri-C_{1-6}$ -alkylsilyl, benzoxazolyl or  $-CH_2OH$ .

30 In another embodiment  $R^{16}$  is hydrogen,  $R^{17}$  is  $C_{1-6}$ -alkyl and  $R^{18}$  is  $-S(O)_2NR^{21}R^{22}$ , wherein  $R^{21}$  is  $C_{1-6}$ -alkyl and  $R^{22}$  is phenyl.

In still another embodiment  $R^{16}$ ,  $R^{17}$  and  $R^{18}$  are selected from hydrogen,  $-OCF_3$ ,  $-CF_3$ ,  $-Br$ ,  $-F$  and  $-Cl$ .

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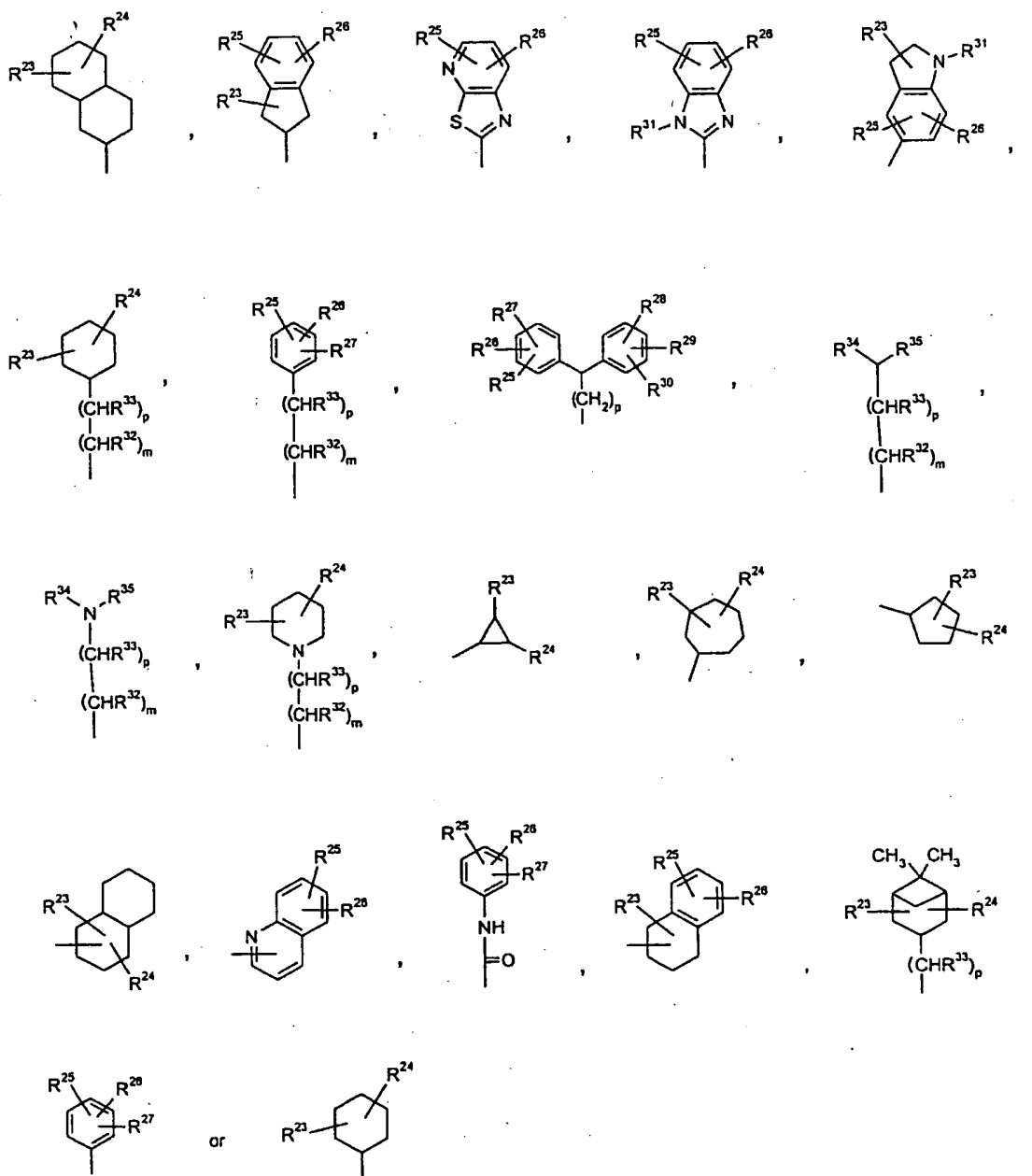
In a preferred embodiment E is



wherein

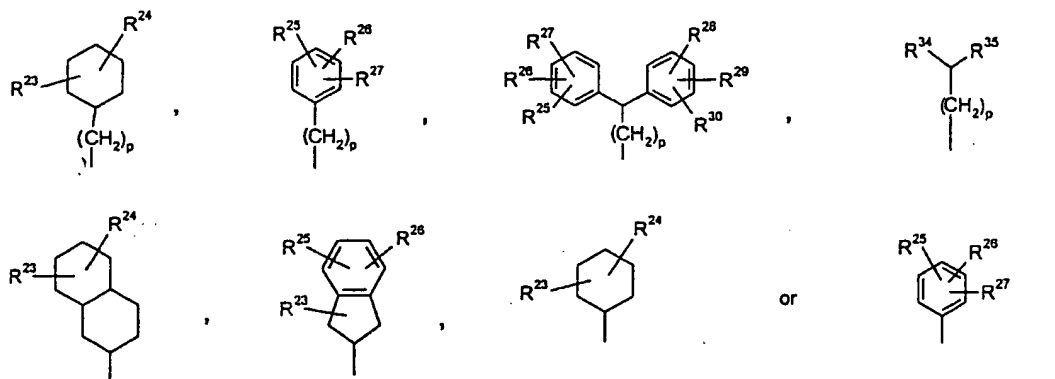
m, p and  $R^{23}$  to  $R^{35}$  are as defined for formula (I).

5 Preferably, E is



wherein m, p and  $R^{23}$  to  $R^{35}$  are as defined for formula (I).

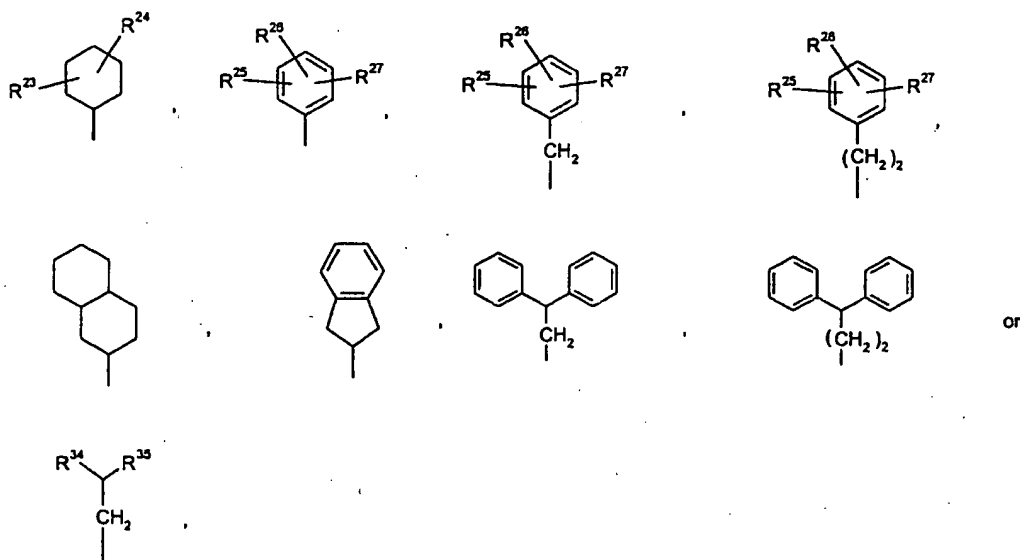
More preferably, E is



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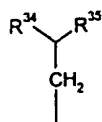
wherein p,  $R^{23}$ ,  $R^{24}$ ,  $R^{25}$ ,  $R^{26}$ ,  $R^{27}$ ,  $R^{28}$ ,  $R^{29}$ ,  $R^{30}$ ,  $R^{34}$  and  $R^{35}$  are as defined for formula (I).

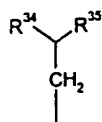
Even more preferably, E is



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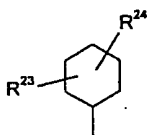
wherein  $R^{23}$ ,  $R^{24}$ ,  $R^{25}$ ,  $R^{26}$ ,  $R^{27}$ ,  $R^{34}$  and  $R^{35}$  are as defined for formula (I).



When E is ,  $R^{34}$  and  $R^{35}$  are preferably independently  $C_{1-6}$ -alkyl, hydrogen or  $C_{1-6}$ -alkoxy. More preferably,  $R^{34}$  and  $R^{35}$  are both  $C_{1-6}$ -alkyl.

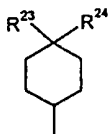
In another preferred embodiment E is

5



wherein  $R^{23}$  and  $R^{24}$  are as defined for formula (I).

10 Preferably, E is



wherein  $R^{23}$  and  $R^{24}$  are as defined for formula (I).

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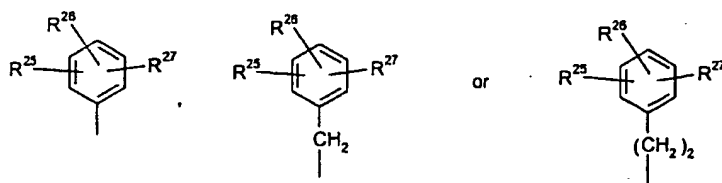
Preferably,  $R^{23}$  and  $R^{24}$  are independently selected from hydrogen,  $C_{1-6}$ -alkyl,  $C_{3-8}$ -cycloalkyl,  $C_{3-8}$ -cycloalkylidene, phenoxy, phenyl,  $-C(O)NR^{36}R^{37}$  and  $-OC(O)NH$ -phenyl, of which the phenyl moiety optionally may be substituted with  $-OCF_3$ , wherein  $R^{36}$  and  $R^{37}$  are as defined in claim 1, or  $R^{23}$  and  $R^{24}$  together form the radical  $-(CH_2)_t-CR^{40}R^{41}-(CH_2)_l-$ ,  $-O-(CH_2)_l-CR^{40}R^{41}-(CH_2)_t-O-$ ,  $-S-(CH_2)_l-CR^{40}R^{41}-(CH_2)_t-S-$ , wherein  $t$ ,  $l$ ,  $R^{40}$  and  $R^{41}$  are as defined for formula (I).

20

More preferably,  $R^{23}$  is hydrogen and  $R^{24}$  is  $C_{1-6}$ -alkyl such as *tert*-butyl or  $C_{3-8}$ -cycloalkyl such as cyclohexyl, wherein  $R^{23}$  and  $R^{24}$  are both  $C_{1-6}$ -alkyl or wherein  $R^{23}$  and  $R^{24}$  together form the radical  $-(CH_2)_5-$ .

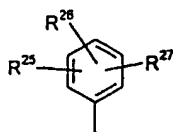
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In yet another preferred embodiment E is



5 wherein  $R^{25}$ ,  $R^{26}$  and  $R^{27}$  are as defined for formula (I).

Preferably, E is



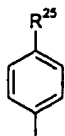
10

wherein  $R^{25}$ ,  $R^{26}$  and  $R^{27}$  are as defined for formula (I).

Preferably,  $R^{25}$ ,  $R^{26}$  and  $R^{27}$  are independently selected from hydrogen, halogen,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy,  $C_{3-8}$ -cycloalkyl,  $C_{4-8}$ -cycloalkenyl,  $-CF_3$ ,  $-OCF_3$  or  $-NR^{42}R^{43}$ , wherein  $R^{42}$  and  $R^{43}$  are as defined for formula (I).

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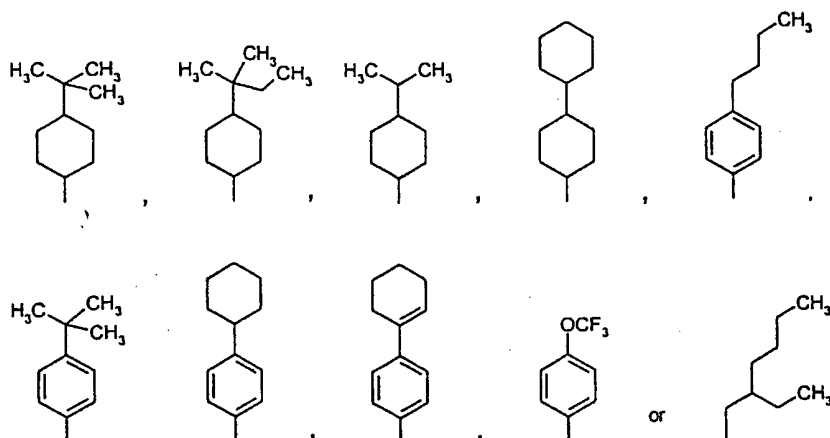
More preferably, E is



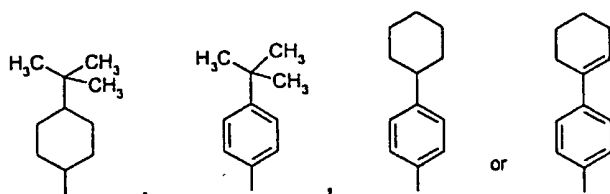
20

wherein  $R^{25}$  is  $-OCF_3$ ,  $-CF_3$ ,  $C_{1-6}$ -alkyl such as *tert*-butyl, piperidyl,  $C_{3-8}$ -cycloalkyl such as cyclohexyl or  $C_{4-8}$ -cycloalkenyl such as cyclohexenyl.

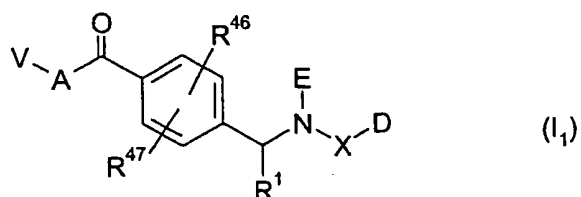
In another preferred embodiment E is



5 Of these E is preferably



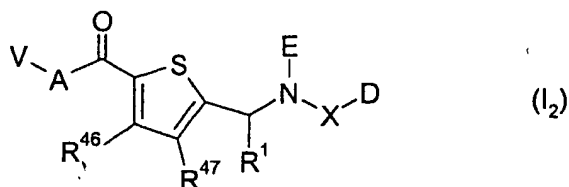
10 In one preferred embodiment the present invention relates to compounds of the general formula (I<sub>1</sub>):



15 wherein V, A, R<sup>46</sup>, R<sup>47</sup>, R<sup>1</sup>, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.



In another preferred embodiment the present invention relates to compounds of the general formula (I<sub>2</sub>):

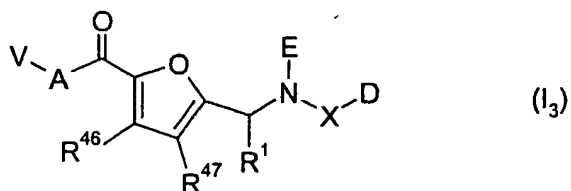


5

wherein V, A, R<sup>46</sup>, R<sup>47</sup>, R<sup>1</sup>, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

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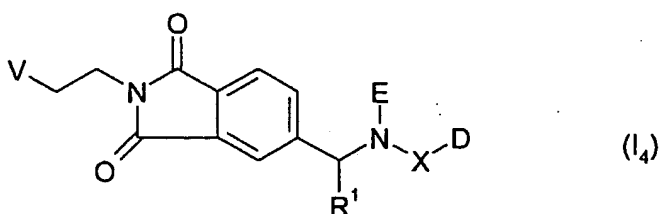
In still another preferred embodiment the present invention relates to compounds of the general formula (I<sub>3</sub>):



15

wherein V, A, R<sup>46</sup>, R<sup>47</sup>, R<sup>1</sup>, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

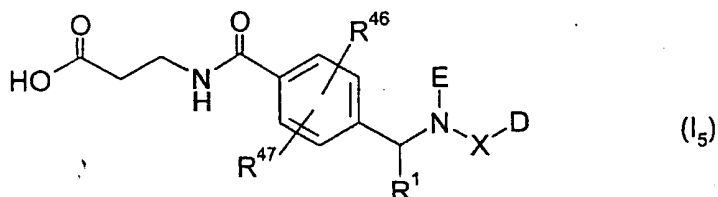
In yet another preferred embodiment the present invention relates to compounds of the general formula (I<sub>4</sub>):



20

wherein V is -C(O)OR<sup>2</sup>, -C(O)NR<sup>2</sup>R<sup>3</sup> or -C(O)NR<sup>2</sup>OR<sup>3</sup>, and R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

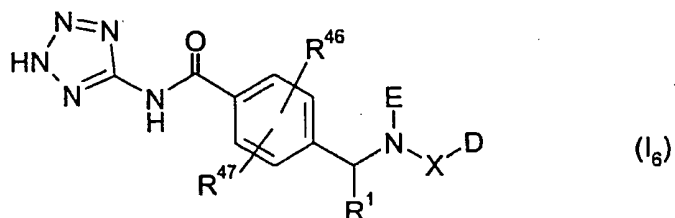
In a further preferred embodiment the present invention relates to compounds of the general formula (I<sub>5</sub>):



5

wherein R<sup>46</sup>, R<sup>47</sup>, R<sup>1</sup>, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

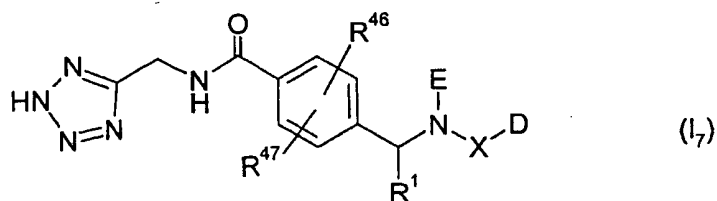
10 In still a further preferred embodiment the present invention relates to compounds of the general formula (I<sub>6</sub>):



15

wherein R<sup>46</sup>, R<sup>47</sup>, R<sup>1</sup>, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

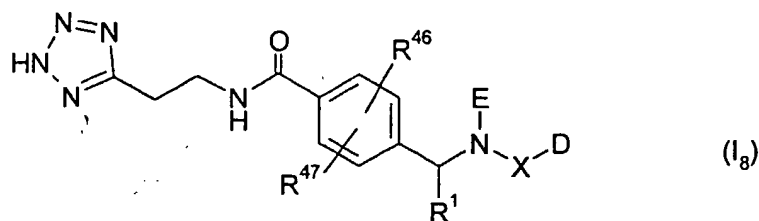
In yet a further preferred embodiment the present invention relates to compounds of the general formula (I<sub>7</sub>):



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wherein R<sup>46</sup>, R<sup>47</sup>, R<sup>1</sup>, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

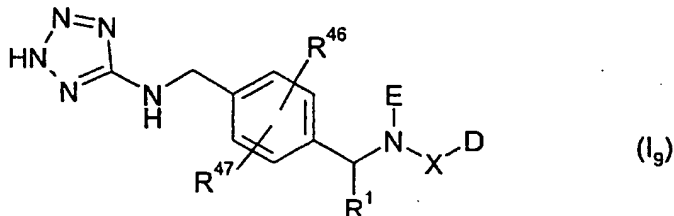
In another preferred embodiment the present invention relates to compounds of the general formula (I<sub>8</sub>):



5

wherein R<sup>46</sup>, R<sup>47</sup>, R<sup>1</sup>, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

- 10 In still another preferred embodiment the present invention relates to compounds of the general formula (I<sub>9</sub>):



- 15 wherein R<sup>46</sup>, R<sup>47</sup>, R<sup>1</sup>, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

In the above formulae (I<sub>1</sub>) to (I<sub>3</sub>) and (I<sub>5</sub>) to (I<sub>9</sub>), R<sup>46</sup> and R<sup>47</sup> are preferably both hydrogen.

- 20 The compounds of the present invention may have one or more asymmetric centres and it is intended that any optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof are included within the scope of the invention.

- 25 Furthermore, when a double bond or a fully or partially saturated ring system is present in the molecule geometric isomers may be formed. It is intended that any geometric isomers, as separated, pure or partially purified geometric isomers or mixtures thereof are included within the scope of the invention. Likewise, molecules having a bond with restricted rotation may

form geometric isomers. These are also intended to be included within the scope of the present invention.

Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms which the compounds are able to form are included within the scope of the present invention.

The present invention also encompasses pharmaceutically acceptable salts of the present compounds. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pantoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methyl-, dimethyl-, trimethyl-, ethyl-, hydroxyethyl-, diethyl-, butyl-, tetramethylammonium salts and the like.

25

Also intended as pharmaceutically acceptable acid addition salts are the hydrates, which the present compounds, are able to form.

Furthermore, the pharmaceutically acceptable salts comprise basic amino acid salts such as lysine, arginine and ornithine.

30

The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

35

The compounds of the present invention may form solvates with standard low molecular weight solvents using methods well known to the person skilled in the art. Such solvates are also contemplated as being within the scope of the present invention.

5

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming pharmacologically active substances. In general, such prodrugs will be functional derivatives of the compounds of the general formula (I), which are readily convertible in vivo into the required compound of the formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

10

The invention also encompasses active metabolites of the present compounds.

15

The compounds according to the present invention act to antagonize the action of glucagon and are accordingly useful for the treatment and/or prevention of disorders and diseases in which such an antagonism is beneficial.

20 Accordingly, in a further aspect the invention relates to a compound according to the invention for use as a medicament.

The invention also relates to pharmaceutical compositions comprising, as an active ingredient, at least one compound according to the invention together with one or more pharmaceutically acceptable carriers or excipients.

25

The pharmaceutical composition is preferably in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg and especially preferred from about 0.5 mg to about 200 mg of the compound according to the invention.

30

Furthermore, the invention relates to the use of a compound according to the invention for the preparation of a pharmaceutical composition for the treatment and/or prevention of a disorder or disease, wherein a glucagon antagonistic action is beneficial.

The invention also relates to a method for the treatment and/or prevention of disorders or diseases, wherein a glucagon antagonistic action is beneficial the method comprising administering to a subject in need thereof an effective amount of a compound according to the invention.

5

Owing to their antagonizing effect of the glucagon receptor the present compounds may be suitable for the treatment and/or prevention of any glucagon-mediated conditions and diseases.

10

Accordingly, the present compounds may be applicable for the treatment and/or prevention of hyperglycemia, IGT, insulin resistance syndromes, syndrome X, Type 1 diabetes, Type 2 diabetes, hyperlipidemia, dyslipidemia, hypertriglyceridemia, glucagonomas, acute pancreatitis, cardiovascular diseases, hypertension, cardiac hypertrophy, gastrointestinal disorders, obesity, diabetes as a consequence of obesity, diabetic dyslipidemia, etc. Furthermore, they may be applicable as diagnostic agents for identifying patients having a defect in the glucagon receptor, as a therapy to increase gastric acid secretions and to reverse intestinal hypomotility due to glucagon administration.

15

In a preferred embodiment of the invention the present compounds are used for the manufacture of a medicament for the treatment and/or prevention of hyperglycemia.

20

In yet a preferred embodiment of the invention the present compounds are used for the manufacture of a medicament for lowering blood glucose in a mammal.

25

In another preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of IGT.

30

In still another preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of Type 2 diabetes.

In yet another preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from IGT to Type 2 diabetes.

In yet another preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

- 5 In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of Type 1 diabetes. Such treatment and/or prevention is normally accompanied by insulin therapy.

- 10 In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of obesity.

In still a further embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of an appetite regulation or energy expenditure disorder.

15

In a further aspect of the invention the present compounds may be administered in combination with one or more pharmacologically active substances eg selected from antidiabetics, antiobesity agents, antihypertensive agents and agents for the treatment and/or prevention of complications resulting from or associated with diabetes.

20

Suitable antidiabetics comprise insulin, GLP-1 derivatives such as those disclosed in WO 98/08871 to Novo Nordisk A/S, which is incorporated herein by reference, as well as orally active hypoglycaemic agents.

25

The orally active hypoglycaemic agents preferably comprise sulphonylureas, biguanides, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon antagonists, GLP-1 agonists, potassium channel openers such as those disclosed in WO 97/26265 and WO 99/03861 to Novo Nordisk A/S which are incorporated herein by reference, insulin sensitizers, DPP-IV (dipeptidyl peptidase-IV) inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, compounds modifying the lipid metabolism such as antihyperlipidemic agents and antilipidemic agents, compounds lowering food intake, PPAR (peroxisome proliferator-activated receptor) and RXR (retinoid X receptor) agonists and agents acting on the ATP-dependent potassium channel of the  $\beta$ -cells.

35

In one embodiment of the invention the present compounds are administered in combination with insulin.

In a further embodiment the present compounds are administered in combination with a  
5 sulphonylurea eg tolbutamide, glibenclamide, glipizide or glicazide.

In another embodiment the present compounds are administered in combination with a biguanide eg metformin.

10 In yet another embodiment the present compounds are administered in combination with a meglitinide eg repaglinide.

In still another embodiment the present compounds are administered in combination with a thiazolidinedione eg troglitazone, ciglitazone, pioglitazone, rosiglitazone or the compounds  
15 disclosed in WO 97/41097 to Dr. Reddy's Research Foundation.

Furthermore, the present compounds may be administered in combination with the insulin sensitizers disclosed in WO 99/19313 to Dr. Reddy's Research Foundation.

20 In a further embodiment the present compounds are administered in combination with an  $\alpha$ -glucosidase inhibitor eg miglitol or acarbose.

In another embodiment the present compounds are administered in combination with an agent acting on the ATP-dependent potassium channel of the  $\beta$ -cells eg tolbutamide, gliben-  
25 clamide, glipizide, glicazide or repaglinide.

Furthermore, the present compounds may be administered in combination with nateglinide.

In still another embodiment the present compounds are administered in combination with an  
30 antihyperlipidemic agent or antilipidemic agent eg cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine.

In a further embodiment the present compounds are administered in combination with more than one of the above-mentioned compounds eg in combination with a sulphonylurea and



metformin, a sulphonylurea and acarbose, repaglinide and metformin, insulin and a sulphonylurea, insulin and metformin, insulin and troglitazone, insulin and lovastatin, etc.

Furthermore, the compounds according to the invention may be administered in combination  
5 with one or more antiobesity agents or appetite regulating agents.

Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4 (melanocortin 4) agonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, uro-  
10 cortin agonists,  $\beta 3$  agonists, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, serotonin re-uptake inhibitors, serotonin and noradrenaline re-uptake inhibitors, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing  
15 compounds, TRH (thyreotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA (dopamine) agonists (bromocriptin, doprexin), lipase/amylase inhibitors, PPAR modulators, RXR modulators or TR  $\beta$  agonists.

In one embodiment of the invention the antiobesity agent is leptin.  
20

In another embodiment the antiobesity agent is dexamphetamine or amphetamine.

In another embodiment the antiobesity agent is fenfluramine or dexfenfluramine.

25 In still another embodiment the antiobesity agent is sibutramine.

In a further embodiment the antiobesity agent is orlistat.

In another embodiment the antiobesity agent is mazindol or phentermine.  
30

Furthermore, the present compounds may be administered in combination with one or more antihypertensive agents. Examples of antihypertensive agents are  $\beta$ -blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril,  
35 quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nifedipine, nicardipine,

isradipine, nimodipine, diltiazem and verapamil, and  $\alpha$ -blockers such as doxazosin, urapidil, prazosin and terazosin. Further reference can be made to Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

- 5 It should be understood that any suitable combination of the compounds according to the invention with one or more of the above-mentioned compounds and optionally one or more pharmacologically active substances are considered to be within the scope of the present invention.

## 10 PHARMACEUTICAL COMPOSITIONS

- The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19<sup>th</sup> Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

- The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

- Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, they can be prepared with coatings such as enteric coatings or they can be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well known in the art.

Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and non-aqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot injectable formulations are also contemplated as being within the scope of the present invention.

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants etc.

A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body weight per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day administered in one or more dosages such as 1 to 3 dosages. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration one or more times per day such as 1 to 3 times per day may contain of from 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg, and more preferred from about 0.5 mg to about 200 mg.

For parenteral routes, such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is an acid addition salt of a compound having the utility of a free base. When a compound of the formula (I) contains a free base such salts are prepared in a conventional manner by treating a solution or suspension of a free base of the formula (I) with a chemical equivalent of a pharmaceutically acceptable acid, for example, inorganic and organic acids. Representative examples are mentioned above. Physiologically acceptable salts of a compound with a hydroxy group include the anion of said compound in combination with a suitable cation such as sodium or ammonium ion.

For parenteral administration, solutions of the novel compounds of the formula (I) in sterile aqueous solution, aqueous propylene glycol or sesame or peanut oil may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatine, agar, pectin, acacia, magnesium stearate, stearic acid or lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethylene or water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The pharmaceutical compositions formed by combining the novel compounds of the formula (I) and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include a suitable excipient. These formulations may be in the form of powder or granules, as a solution or suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion.

If a solid carrier is used for oral administration, the preparation may be tableted, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

A typical tablet that may be prepared by conventional tableting techniques may contain:

## Core:

	Active compound (as free compound or salt thereof)	5.0 mg
	Lactosum Ph. Eur.	67.8 mg
	Cellulose, microcryst. (Avicel)	31.4 mg
5	Amberlite	1.0 mg
	Magnesii stearas Ph. Eur.	q.s.

## Coating:

	HPMC approx.	9 mg
10	Mywacett 9-40 T* approx.	0.9 mg

\*Acylated monoglyceride used as plasticizer for film coating.

If desired, the pharmaceutical composition of the invention may comprise the compound of  
15 the formula (I) in combination with further pharmacologically active substances such as those  
described in the foregoing.

**EXPERIMENTAL**

20 In the following section binding assays as well as functional assays useful for evaluating the  
efficiency of the compounds of the invention are described.

Binding of compounds to the glucagon receptor was determined in a competition binding as-  
say using the cloned human glucagon receptor.

25 Antagonism was determined as the ability of the compounds to inhibit the amount of cAMP  
formed in the presence of 5 nM glucagon.

For further characterization, antagonism was determined in a functional assay, measured as  
30 the ability of the compounds to right-shift the glucagon dose-response curve. Using at least 3  
different antagonist concentrations, the  $K_i$  was calculated from a Schild plot.

Glucagon Binding Assay (I)

Receptor binding was assayed using cloned human receptor (Lok et al., Gene 140, 203-209  
35 (1994)). The receptor inserted in the pLJ6' expression vector using EcoRI/Sst1 restriction sites

(Lok et al.) was expressed in a baby hamster kidney cell line (A3 BHK 570-25). Clones were selected in the presence of 0.5 mg/mL G-418 and were shown to be stable for more than 40 passages. The  $K_d$  was shown to be 0.1 nM.

- 5 Plasma membranes were prepared by growing cells to confluence, detaching them from the surface and resuspending the cells in cold buffer (10 mM tris/HCl, pH 7.4 containing 30 mM NaCl, 1 mM dithiothreitol, 5 mg/L leupeptin (Sigma), 5 mg/L pepstatin (Sigma), 100 mg/L bacitracin (Sigma) and 15 mg/L recombinant aprotinin (Novo Nordisk A/S)), homogenization by two 10-s bursts using a Polytron PT 10-35 homogenizer (Kinematica), and centrifugation upon a  
10 layer of 41 w/v % sucrose at 95.000 x g for 75 min. The white band located between the two layers was diluted in buffer and centrifuged at 40.000 x g for 45 min. The precipitate containing the plasma membranes was suspended in buffer and stored at -80°C until use.

- 15 Glucagon was iodinated according to the chloramine T method (Hunter and Greenwood, Nature 194, 495 (1962)) and purified using anion exchange chromatography (Jørgensen et al., Hormone and Metab. Res. 4, 223-224 (1972). The specific activity was 460  $\mu\text{Ci}/\mu\text{g}$  on the day of iodination. Tracer was stored at -18°C in aliquots and were used immediately after thawing.

- 20 Binding assays were carried out in triplicate in filter microtiter plates (MADV N65, Millipore). The buffer used in this assay was 50 mM HEPES, 5 mM EGTA, 5 mM  $\text{MgCl}_2$ , 0.005% tween 20, pH 7.4. Glucagon was dissolved in 0.05 M HCl, added an equal amount (w/w) of HSA and freeze-dried. On the day of use, it was dissolved in water and diluted in buffer to the desired concentrations.

- 25 Test compounds were dissolved and diluted in DMSO. 140  $\mu\text{L}$  buffer, 25  $\mu\text{L}$  glucagon or buffer, and 10  $\mu\text{L}$  DMSO or test compound were added to each well. Tracer (50.000 cpm) was diluted in buffer and 25  $\mu\text{L}$  were added to each well. 1-4  $\mu\text{g}$  freshly thawed plasma membrane protein diluted in buffer was then added in aliquots of 25  $\mu\text{L}$  to each well. Plates were incubated at 30°C for 2 hours. Non-specific binding was determined with  $10^{-6}$  M of glucagon. Bound tracer and un-  
30 bound tracer were then separated by vacuum filtration (Millipore vacuum manifold). The plates were washed with 2 x 100  $\mu\text{L}$  buffer/ well. The plates were air dried for a couple of hours, whereupon the filters were separated from the plates using a Millipore Puncher. The filters were counted in a gamma counter.

### Functional Assay (I)

The functional assay was carried out in 96 well microtiter plates (tissue culture plates, Nunc). The resulting buffer concentrations in the assay were 50 mM tris/HCl, 1 mM EGTA, 1.5 mM MgSO<sub>4</sub>, 1.7 mM ATP, 20  $\mu$ M GTP, 2 mM IBMX (isobutyl-methyl-xanthine), 0.02% tween-20 and 0.1% HSA. pH was 7.4. Glucagon and proposed antagonist were added in aliquots of 35  $\mu$ L diluted in 50 mM tris/HCl, 1 mM EGTA, 1.85 mM MgSO<sub>4</sub>, 0.0222 % tween-20 and 0.111 % HSA, pH 7.4; 20  $\mu$ L of 50 mM tris/HCl, 1 mM EGTA, 1.5 mM MgSO<sub>4</sub>, 11.8 mM ATP, 0.14 mM GTP, 14 mM IBMX and 0.1% HSA, pH 7.4 was added. GTP was dissolved immediately before the assay.

50  $\mu$ L containing 5  $\mu$ g of plasma membrane protein was added in a tris/HCl, EGTA, MgSO<sub>4</sub>, HSA buffer (the actual concentrations were dependent upon the concentration of protein in the stored plasma membranes).

The total assay volume was 140  $\mu$ L. The assay was incubated for 2 hours at 37°C with continuous shaking. Reaction was terminated by addition of 25  $\mu$ L 0.5 N HCl. cAMP was measured by the use of a scintillation proximity kit (Amersham).

### Glucagon Binding Assay (II)

Receptor binding was assayed using the cloned human receptor (Lok et al., Gene 140, 203-209 (1994)). The receptor inserted in the pLJ6' expression vector using EcoRI/SstI restriction sites (Lok et al.) was expressed in a baby hamster kidney cell line (A3 BHK 570-25). Clones were selected in the presence of 0.5 mg/mL G-418 and were shown to be stable for more than 40 passages. The K<sub>d</sub> was shown to be 0.1 nM.

Plasma membranes were prepared by growing cells to confluence, detaching them from the surface and resuspending the cells in cold buffer (50 mM tris base, pH 7.4 containing 0.32 mM sucrose, 2 mM EGTA, 1  $\mu$ g/mL leupeptin, 5  $\mu$ g/mL pepstatin A, 5  $\mu$ g/mL aprotinin, 1 mM phenylmethylsulfonylfluoride (all from Sigma)), homogenization by two 10-s bursts using a Polytron PT 10-35 homogenizer (Kinematica), and centrifugation. The homogenate was resuspended and centrifuged again. The final precipitate containing the plasma membranes was suspended in buffer and stored at -80°C until use.

Binding assays were carried out in duplicate in polypropylene tubes or microtiter plates. The buffer used in this assay was 50 mM HEPES pH 7.4 containing 5 mM EGTA, 5 mM MgCl<sub>2</sub> and

0.005% Tween 20. Sample (glucagon (Bachem CA) or test compounds) was added to each tube or well. Tracer (~ 25,000 cpm) was diluted in buffer and was added to each tube or well. 0.5 mg freshly thawed plasma membrane protein diluted in buffer was then added in aliquots to each tube or well. Tubes or plates were incubated at 37°C for 1 hour. Non-specific binding was  
5 determined with  $10^{-7}$  M of glucagon. Bound tracer and unbound tracer were then separated by vacuum filtration. The tubes or wells were washed twice with 0.01% Triton X-100 buffer. Scintillation fluid was added to the plates and radioactivity was quantified using a scintillation counter.

#### Functional Assay (II)

10 The functional assay determined the ability of the compounds to antagonize glucagon-stimulated formation of cAMP in a whole-cell assay. The assay was carried out in borosilicate glass 12 x 75 tubes. The buffer concentrations in the assay were 10 mM HEPES, 1 mM EGTA, 1.4 mM  $MgCl_2$ , 0.1 mM IBMX, 30 mM NaCl, 4.7 mM KCl, 2.5 mM  $NaH_2PO_4$ , 3mM glucose and 0.2% BSA. The pH was 7.4. Loose whole cells (0.5 mL,  $10^6/mL$ ) were pretreated with various  
15 concentrations of compounds for 10 min at 37°C, then challenged with glucagon for 20 min. Some aliquots (500  $\mu$ L) of cells were treated with test compounds (55  $\mu$ L) alone to test for agonist activity. The reactions were terminated by centrifugation, followed by cell lysis with the addition of 500  $\mu$ L 0.1% HCl. Cellular debris was pelleted and the supernatant containing cAMP  
20 evaporated to dryness. cAMP was measured by the use of an RIA kit (NEN, NEK-033). Some assays were carried out utilizing the adenylate cyclase FlashPlate system from NEN.

#### Glucagon Binding Assay (III)

BHK (baby hamster kidney cell line) cells were transfected with the human glucagon receptor and a membrane preparation of the cells was prepared. Wheat Germ Agglutinin derivatized  
25 SPA beads containing a scintillant (WGA beads) (Amersham) bound the membranes.  $^{125}I$ -glucagon bound to human glucagon receptor in the membranes and excited the scintillant in the WGA beads to light emission. Glucagon or samples binding to the receptor competed with  $^{125}I$ -glucagon.

30 All steps in the membrane preparation were kept on ice or performed at 4°C. BHK cells were harvested and centrifuged. The pellet was resuspended in homogenisation buffer (25 mM HEPES pH = 7.4, 2.5 mM  $CaCl_2$ , 1.0 mM  $MgCl_2$ , 250 mg/L bacitracin), homogenised 2 x 10 sec using Polytron 10-35 homogenizer (Kinematica) and added the same amount of homogenisation buffer as used for resuspension. After centrifugation (15 min at 1000 x g) the su-  
35 pernatant was transferred to cold centrifuge tubes and centrifuged for 45 min at 40,000 x g.



The pellet was resuspended in homogenisation buffer, homogenised 2 x 10 sec (Polytron) and additional homogenisation buffer was added. The suspension was centrifuged for 45 min at 40.000 x g and the pellet was resuspended in resuspension buffer (25 mM HEPES pH = 7.4, 2.5 mM CaCl<sub>2</sub>, 1.0 mM MgCl<sub>2</sub>) and homogenised 2 x 10 sec. (Polytron). The protein concentration was normally around 1.75 mg/mL. Stabilisation buffer (25 mM HEPES pH = 7.4, 2.5 mM CaCl<sub>2</sub>, 1.0 mM MgCl<sub>2</sub>, 1% BSA, 500 mg/L bacitracin, 2.5 M sucrose) was added and the membrane preparation was stored at -80°C.

The glucagon binding assay was carried out in opti plates (Polystyrene Microplates, Packard). 50 µL assay buffer (25 mM HEPES pH = 7.5, 2.5 mM CaCl<sub>2</sub>, 1.0 mM MgCl<sub>2</sub>, 0.003% Tween-20, 0.005% bacitracin, 0.05% sodium azide) and 5 µL glucagon or test compound (in DMSO) were added to each well. 50 µL tracer (<sup>125</sup>I-porcine glucagon, 70.000 cpm) and 50 µL membranes (12.5 µg) containing the human glucagon receptor were then added to the wells. Finally 50 µL WGA beads containing 1 mg beads were transferred to the well. The assay was incubated for 4 hours on a shaker and then settled for 8-48 hours. The opti plates were counted in a Topcounter. Non-specific binding was determined with 500 nM of glucagon.

#### Synthesis methods

The following synthesis protocols refer to intermediate compounds and final products identified in the specification and in the synthetic schemes. The preparation of the compounds of the present invention is described in detail using the following examples, but the chemical reactions described are disclosed in terms of their general applicability to the preparation of the glucagon antagonists of the invention. Occasionally, the reaction may not be applicable as described to each compound included within the disclosed scope of the invention. The compounds for which this occurs will be readily recognised by those skilled in the art. In these cases the reactions can be successfully performed by conventional modifications known to those skilled in the art, that is, by appropriate protection of interfering groups, by changing to other conventional reagents, or by routine modification of reaction conditions. Alternatively, other reactions disclosed herein or otherwise conventional will be applicable to the preparation of the corresponding compounds of the invention. In all preparative methods, all starting materials are known or may easily be prepared from known starting materials. All temperatures are set forth in degrees Celsius and unless otherwise indicated, all parts and percentages are by weight when referring to yields and all parts are by volume when referring to solvents and eluents.

Some of the NMR data shown in the following examples are only selected data.

Unless otherwise specified in the examples, the *cis/trans* isomeric compounds were obtained as mixtures of *cis* and *trans* isomers, which may be separated by chromatography. Thus, the present invention comprises the compounds in form of mixtures of *cis* and *trans* isomers as well as the pure isomeric forms.

In the examples the following terms are intended to have the following meanings:

DMF:	<i>N,N</i> -dimethylformamide
DMSO:	dimethyl sulfoxide
Fmoc:	9-fluorenylmethyloxycarbonyl
HBTU:	2-(1 <i>H</i> -Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
M.p.:	melting point
NCS:	<i>N</i> -Chlorosuccinimide
NMP:	<i>N</i> -methylpyrrolidone
-OSu:	2,5-dioxo-pyrrolidin-1-yloxy
TFA:	trifluoroacetic acid
THF:	tetrahydrofuran

10

The final products obtained were characterized by analytical RP-HPLC (retention time) and/or by HPLC-MS (molecular mass and/or retention time).

15

The RP-HPLC analyses were performed on a Waters HPLC system consisting of Waters™ 600S Controller, Waters™ 996 Photodiode Array Detector, Waters™ 717 Autosampler, Waters™ 616 Pump, Waters™ 3 mm x 150 mm 3.5 μ C-18 Symmetry column and Millenium QuickSet Control Ver. 2.15 using UV detection at 214 nm. A linear gradient was applied from 5% to 90% acetonitrile/0.1% TFA/water over 15 min at a flow rate of 1 mL/minute.

20

#### HPLC-MS (METHOD A):

The following instrumentation was used:

- Sciex API 100 Single quadropole mass spectrometer
- Perkin Elmer Series 200 Quard pump
- Perkin Elmer Series 200 autosampler

- Applied Biosystems 785A UV detector
- Sedex 55 evaporative light scattering detector
- A Valco column switch with a Valco actuator controlled by timed events from the pump.

- 5 The Sciex Sample control software running on a Macintosh PowerPC 7200 computer was used for the instrument control and data acquisition.

The HPLC pump was connected to four eluent reservoirs containing:

- A: Acetonitrile  
B: Water  
C: 0.5 % TFA in water  
D: 0.02 M ammonium acetate

10

The requirements for samples are that they contain approximately 500 µg/mL of the compound to be analysed in an acceptable solvent such as methanol, ethanol, acetonitrile, THF, water and mixtures thereof. (High concentrations of strongly eluting solvents will interfere with the chromatography at low acetonitrile concentrations.)

15

The analysis was performed at room temperature by injecting 20 µL of the sample solution on the column, which was eluted with a gradient of acetonitrile in either 0.05% TFA or 0.002 M ammonium acetate. Depending on the analysis method varying elution conditions were used.

20

The eluate from the column was passed through a flow splitting T-connector, which passed approximately 20 µL/min (1/50) through approx. 1 m. 75 µ fused silica capillary to the API interface of API 100 spectrometer.

- 25 The remaining 1.48 mL/min (49/50) was passed through the UV detector and to the ELS detector.

During the LC-analysis the detection data were acquired concurrently from the mass spectrometer, the UV detector and the ELS detector.

30

The LC conditions, detector settings and mass spectrometer settings used for the different

methods are given in the following tables.

Column	Waters Symmetry C <sub>18</sub> 3 mm x 150 mm		
Gradient	5% - 90% acetonitrile in 0.05% TFA linearly during 15 min at 1 mL/min		
Detection	UV: 214 nm	ELS: 40°C	
MS	Experiment:	Start: 100 amu	Stop: 800 amu Step: 0.2 amu
	Dwell:	0.571 msec	
	Method:	Scan 284 times = 9.5 min	

5 HPLC-MS (METHOD B):

This method was identical to METHOD A but using the following conditions and settings:

Column	YMC ODS-A 120Å s - 5µ 3 mm x 50 mm id		
Gradient	5% - 90% acetonitrile in 0.05% TFA linearly during 7.5 min at 1.5 mL/min		
Detection	UV: 214 nm	ELS: 40°C	
MS	Experiment:	Start: 100 amu	Stop: 800 amu Step: 0.2 amu
	Dwell:	0.571 msec	
	Method:	Scan 284 times = 9.5 min	

10 HPLC-MS (METHOD C):

The following instrumentation was used:

- Hewlett Packard series 1100 MSD G1946A Single quadropole mass spectrometer
- Hewlett Packard series 1100 MSD G1312A Bin pump
- Hewlett Packard series 1100 MSD G1313A ALS autosampler
- 15 • Hewlett Packard series 1100 MSD G1315A DAD diode array detector

The HP LC/MSD ChemStation control software running on a HP Vectra computer was used for the instrument control and data acquisition.

The HPLC pump was connected to two eluent reservoirs containing:

- A: 0.05% TFA in water  
B: Acetonitrile

The analysis was performed at room temperature by injecting 1  $\mu$ L of the sample solution on the column which was eluted with a gradient of acetonitrile in 0.05% TFA.

The HPLC conditions, detector settings and mass spectrometer settings used are given in the following table.

Column	Grom Nucleosil 100 C18, 3 $\mu$ m, 2 mm x 60 mm
Gradient	10% - 100% acetonitrile in 0.05% TFA linearly during 5.8 min at 0.6 mL/min
Detection	UV: 210 nm (diode array)
MS	Ionisation mode: API-ES Experiment: Start: 100 amu Stop: 1000 amu Step: 0.1 amu

#### HPLC-MS (METHOD D):

The following instrumentation was used:

- Hewlett Packard series 1100 G1312A Bin Pump
- Hewlett Packard series 1100 G13 15A DAD diode array detector
- Sciex 300 triplequadropole mass spectrometer
- Gilson 215 micro injector
- Sedex 55 evaporative light scattering detector

Pumps and detectors were controlled by MassChrom 1.1.1 software running on a Macintosh G3 computer. Gilson Unipoint Version 1.90 controls the auto-injector.

The HPLC pump was connected to two eluent reservoirs containing:

- A: 0.01% TFA in water  
B: 0.01% TFA in acetonitrile

The analysis was performed at room temperature by injecting an appropriate volume of the sample (preferably 1  $\mu$ L) onto the column that was eluted with a gradient of acetonitrile.

The HPLC conditions, detector settings and mass spectrometer settings used are:

5

Column	YMC ODS-A 120Å s 5 $\mu$ 3 mm X 50 mm id
Gradient	5% - 90% acetonitrile linearly during 7.5 min at 1.5 ml/min
Detection	210 nm (analog output from DAD)
MS	Ionisation mode: API-ES Scan 100-1000 amu step 0.1 amu

#### HPLC-MS (METHOD E):

The following instrumentation was used:

- 10
- Hewlett Packard series 1100 MSD G1946A Single quadropole mass spectrometer
  - Hewlett Packard series 1100 MSD G1312A Bin pump
  - Hewlett Packard series 1100 MSD G1313A ALS autosampler
  - Hewlett Packard series 1100 MSD G1315A DAD diode array detector
- 15
- The HP LC/MSD ChemStation control software running on a HP Vectra computer was udes for the instrument control and data acquisition.

The HPLC pump was connected to two eluent reservoirs containing:

A: 0.01% TFA in water

B: Acetonitrile

- 20
- The analysis was performed at room temperature by injecting 1  $\mu$ L of the sample solution on the column which was eluted with a gradient of acetonitrile in 0.01% TFA.

The HPLC conditions, detector settings and mass spectrometer settings used are given in the following table.

Column	Waters Xterra 100A MS C-18 3.5 $\mu$ m, 2 mm x 50 mm
Gradient	10% - 100% acetonitrile in 0.05% TFA linearly during 4.5 min at 1.5 mL/min
Detection	UV: 210 nm (diode array)
MS	Ionisation mode: API-ES Experiment: Start: 100 amu Stop: 1000 amu Step: 0.1 amu

5

#### HPLC-MS (Method F):

The following instrumentation was used:

- Hewlett Packard series 1100 G1312A Bin Pump
- Hewlett Packard series 1100 Column compartment
- 10 • Hewlett Packard series 1100 G13 15A DAD diode array detector
- Hewlett Packard series 1100 MSD

The instrument was controlled by HP Chemstation software.

- 15 The HPLC pump was connected to two eluent reservoirs containing:

A: 0.01% TFA in water  
B: 0.01% TFA in acetonitrile

The analysis was performed at 40°C by injecting an appropriate volume of the sample (preferably 1  $\mu$ L) onto the column, which was eluted with a gradient of acetonitrile.

- 20 The HPLC conditions, detector settings and mass spectrometer settings used are given in the following table.

Column	Waters Xterra MS C-18 X 3 mm id
Gradient	10% - 100% acetonitrile linearly during 7.5 min at 1.0 mL/min
Detection	UV: 210 nm (analog output from DAD)
MS	Ionisation mode: API-ES Scan 100-1000 amu step 0.1 amu

The compounds of the present invention may be purified using one of the following HPLC methods:

5 Hit fractionation method I

HPLC purification/fractionation of hits is performed on Nucleosil C-18 7  $\mu$ m 8 x 100 mm columns (packed by Grom). A standard gradient with water/acetonitrile added 0.01% TFA is used. Flow rate 9 mL/min starting at 10% organic modifier ending after 18 min on 100% organic modifier. This condition is kept for 1 min. Fractions of 4 mL are collected in a deep well  
10 collection plate.

Equipment:

2 Gilson 306 pumps equipped with 25 mL SC pump heads, Gilson 806 manometer and Gilson 811c dynamic mixing chamber. UV detection is performed with Gilson 119 UV/VIS de-  
15 tector. Gilson 215 Nebula is used as combined injector and fraction collector.

Hit fractionation method II

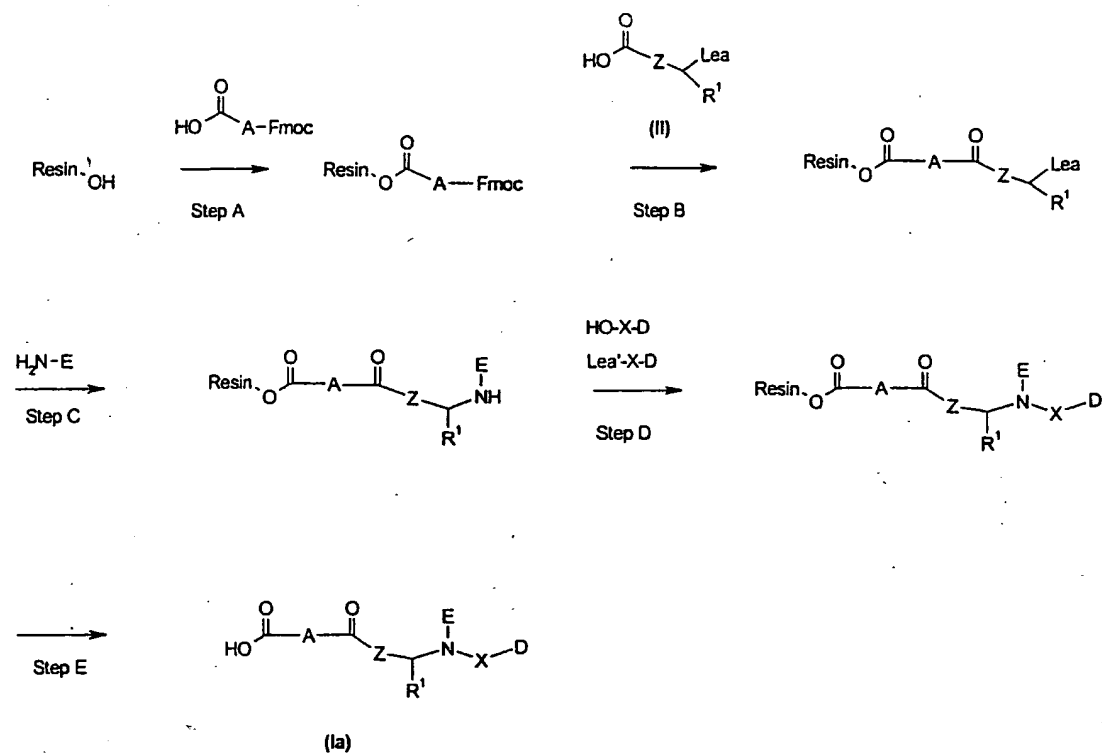
HPLC purification/fractionation of hits is performed on Waters Xterra columns MS C<sub>18</sub> 5  $\mu$ m 7.8 x 100 mm columns. A standard gradient with water/acetonitrile added 0.01% TFA is  
20 used. Flow rate 15 mL/min starting at 10% organic modifier ending after 11 min on 100% modifier. This condition is kept for 1 min. Fractions of 4 mL are collected in a deep well collection plate.

Equipment:

25 1 Gilson 321 pump equipped with 15 mL H1 pumping heads. UV detection is performed with Gilson 119 UV/VIS detector. Gilson 215 Nebula is used as combined injector and fraction collector.



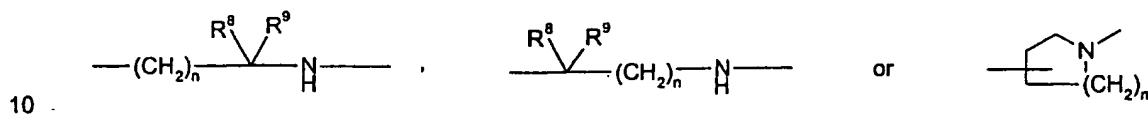
General procedure (A) for the solid phase synthesis of compounds of the general formula (Ia):



5 wherein

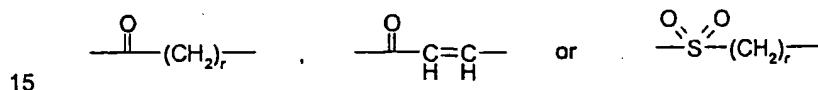
$\text{R}^1$ , Z, E and D are as defined for formula (I),

A is



wherein  $\text{R}^8$  and  $\text{R}^9$  are as defined for formula (I),

X is



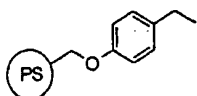
wherein r is as defined for formula (I),

Lea is a leaving group such as chloro, bromo, iodo, mesyl or tosyl,

Lea' is a leaving group such as -OSu, chloro, phenoxy or 4-nitrophenoxy, and

5

Resin denotes a polystyrene resin with a linker such as the Wang linker:



10 wherein PS denotes polystyrene.

Step A:

The reaction is known (Wang S. J., J. Am. Chem. Soc. 95, 1328, 1973) and is generally performed by stirring polystyrene resin loaded with a linker such as the Wang linker with a 4-10 molar excess of Fmoc-protected amino acid activated with a 2-5 molar excess of diisopropylcarbodiimide or dicyclohexylcarbodiimide in the presence of a catalyst such as *N,N*-4-dimethylaminopyridine. The esterification is carried out in a solvent such as THF, dioxane, toluene, dichloromethane, DMF, NMP or a mixture of two or more of these. The reactions are performed between 0°C to 80°C, preferably between 20°C to 40°C. When the esterification is complete excess of reagents is removed by filtration. The resin is successively washed with the solvent used in the reaction, followed by washings with methanol. The resin bound product can be further dried and analyzed.

20

Step B:

25 *N*-Fluorenylmethyloxycarbonyl protection group is removed by treating the resin bound derivative with a 20%-50% solution of a secondary amine such as piperidine in a polar solvent such as DMF or NMP (Carpino L., Han G., J. Org. Chem. 37, 3404, 1972). The reaction is performed between 20°C and 180°C, preferably between 20°C and 40°C. The deprotection can be quantitated by the absorbance of piperidine-dibenzofulvene adduct released from the resin (The combinatorial index, Ed. Bunin B. A., 1998, Academic press, p. 219). When the reaction is complete excess of reagents is removed by filtration. The resin is successively washed with solvent used in the reaction. The resulting resin bound intermediate is acylated with acid (II). The acylation is known (The combinatorial index, Ed. Bunin B. A., 1998, Academic press, p. 78) and is generally performed by stirring resin bound intermediate with a 2-5 molar excess of acid (II)

30

activated with a 2-5 molar excess of diisopropylcarbodiimide or dicyclohexylcarbodiimide in the presence of a side reaction inhibitor such as *N*-hydroxybenzotriazole. The acylation is carried out in a solvent such as THF, dioxane, toluene, dichloromethane, DMF, NMP or a mixture of two or more of these. The reactions are performed between 0°C and 80°C, preferably between 20°C and 40°C. When the acylation is complete excess of reagents is removed by filtration. The resin is successively washed with the solvent used in the reaction, followed by washings with methanol. The resin bound product can be further dried and analyzed.

Step C:

The reaction is known (The combinatorial index, Ed. Bunin B. A., 1998, Academic press, p. 112) and is generally performed by stirring the resin bound intermediate obtained in step B with a 10-20 molar excess of amine. The nucleophilic displacement is carried out in a solvent such as DMSO, DMF, NMP or a mixture of two or more of these. The reaction is performed between 20°C and 120°C, preferably between 60°C and 80°C. When the reaction is complete excess of reagents is removed by filtration. The resin is successively washed with the solvent used in the reaction, followed by washings with methanol. The resin bound product can be further dried and analyzed.

Step D:

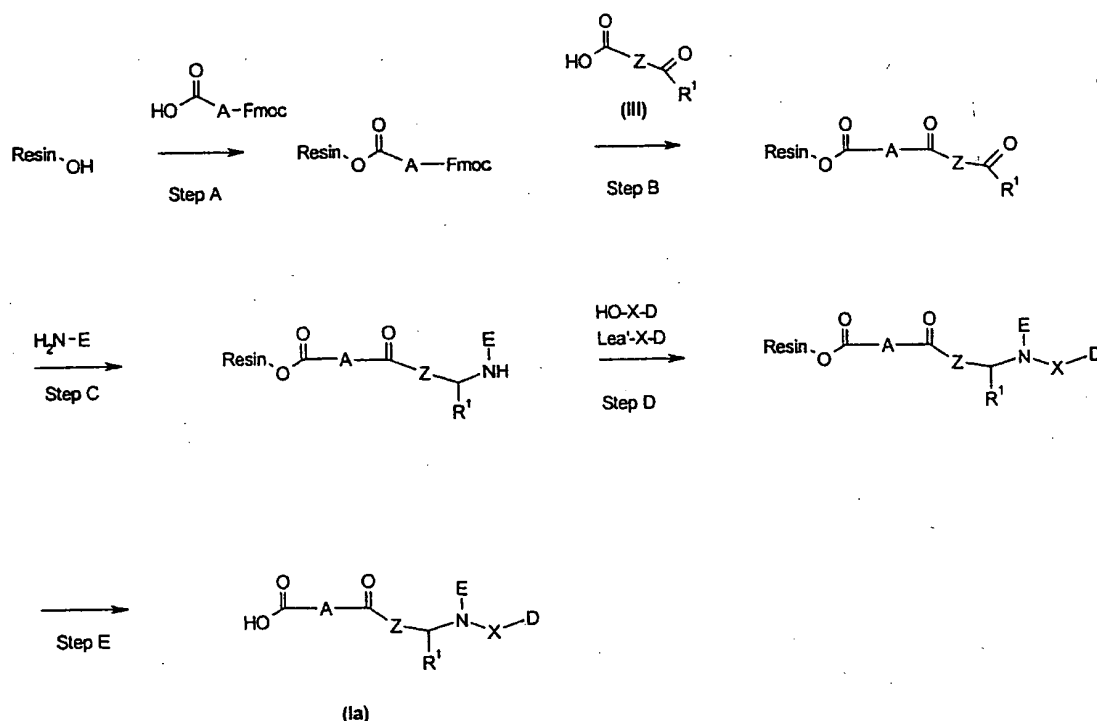
The reaction is known (The combinatorial index, Ed. Bunin B. A., 1998, Academic press, p. 78) and is generally performed by stirring the resin bound intermediate obtained in step C with a 4-10 molar excess of acid HO-X-D activated with a 2-5 molar excess of diisopropylcarbodiimide or dicyclohexylcarbodiimide in the presence of a catalyst such as pyridine and/or 4-dimethylamino-pyridine. The reaction is carried out in a solvent such as THF, dioxane, toluene, dichloromethane, DMF, NMP or a mixture of two or more of these. The reactions are performed between 0°C and 80°C, preferably between 20°C and 40°C. When the reaction is complete excess of reagents is removed by filtration. Alternatively, a solution of Lea'-X-D in an appropriate solvent such as acetonitrile, toluene, DMF, NMP, THF, dichloromethane, 1,2-dichloroethane or DMSO or a mixture of two or more of these, is added and the mixture is vortexed in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine or potassium carbonate under heating, if necessary. The resin is successively washed with solvent used in the reaction, followed by washings with dichloromethane.

Step E:

The reaction is known (The combinatorial index, Ed. Bunin B. A., 1998, Academic press, p. 21) and is generally performed by stirring resin bound intermediate obtained in step D with a 50-95% solution of TFA. The final cleavage is carried out in a solvent such as THF, dichloromethane, 1,2-dichloroethane, 1,3-dichloropropane, toluene or a mixture of two or more of these. The reaction is performed between 0°C and 80°C, preferably between 20°C and 40°C. When the reaction is complete the product is removed by filtration. The resin is successively washed with dichloromethane. The product and washings are collected. The solvent is removed and the product is dried in vacuo. The residue is dissolved in a 1:1 mixture of methanol and dichloromethane (1 mL) and concentrated in vacuo. The product (Ia) is dried in vacuo overnight.

General procedure (B) for the solid phase synthesis of compounds of the general formula (Ia):

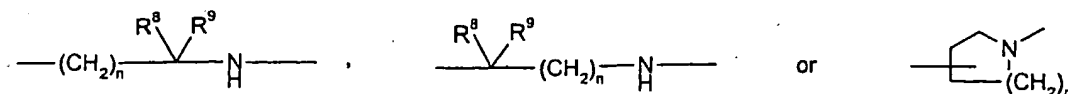
Alternatively, steps B and C of procedure (A) can be modified so that step C is a reductive amination of a resin bound aldehyde or ketone:



20 wherein

R<sup>1</sup>, Z, E and D are as defined for formula (I),

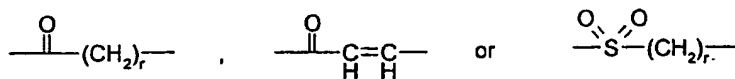
A is



5

wherein R<sup>8</sup> and R<sup>9</sup> are as defined for formula (I),

X is



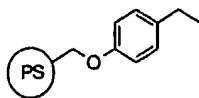
10

wherein r is as defined for formula (I),

Lea' is a leaving group such as -OSu, chloro, phenoxy or 4-nitrophenoxy, and

15

Resin denotes a polystyrene resin with a linker such as the Wang linker:



20

wherein PS denotes polystyrene.

#### Step B:

This step is identical to step B of general procedure (A) with the modification that acid (III) is used instead of acid (II).

25

#### Step C:

The reaction is generally known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 133) and is generally performed by stirring resin bound aldehyde or ketone with an excess of amine at low pH (by addition of an acid, such as acetic acid or formic acid) in a solvent such as THF, DMF, NMP, methanol, ethanol, DMSO, dichloromethane, 1,2-dichloroethane, trimethyl orthoformate, triethyl orthoformate, or a mixture of two or more of these. A

30

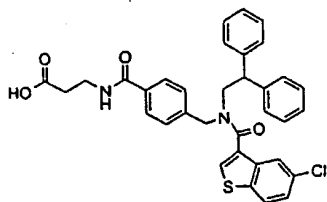
reducing agent such as sodium cyanoborohydride may be used. The reaction is performed between 20°C and 120°C, preferably at 25°C.

The following examples 1 to 9 were prepared according to general procedure (A).

5

EXAMPLE 1 (general procedure (A))

3-(4-((N-(5-Chlorobenzo[b]thiophen-3-carbonyl)-N-(2,2-diphenylethyl)amino)methyl)benzoyl-amino)propionic acid



10

Step A: Resin bound Fmoc-3-aminopropionic acid

Polystyrene resin loaded with the Wang linker (1.07 mmol/g, 25.0 g, 26.75 mmol) was treated overnight at 25°C with a solution of *N*-Fmoc-3-aminopropionic acid (33.3 g, 107 mmol) in 100 mL THF activated with diisopropylcarbodiimide (8.5 mL, 54 mmol) in the presence of 4-dimethylaminopyridine (0.2 g). Excess of reagents was removed by filtration. The resin bound intermediate was successively washed with 3 x 100 mL THF, 3 x 100 mL DMF and 3 x 100 mL methanol. The resin was dried overnight in vacuo at 50°C for 16 hours to afford 31.54 g resin bound Fmoc-3-aminopropionic acid.

20

A small sample of resin bound intermediate (25 mg) was withdrawn and treated with 50% TFA in dichloromethane for 30 min. The resin was drained and washed with dichloromethane several times. The combined filtrates were concentrated in vacuo. The residue was diluted with 10 mL acetonitrile and analyzed by HPLC. The yield was calculated from HPLC trace at 214 nm compared to the solution of a standard.

25

Step B: Resin bound 3-[4-(bromomethyl)benzoyl]aminopropionic acid

The above resin bound Fmoc-3-aminopropionic acid (3.95 g, 2.4 mmol) was treated with 40 mL 50% piperidine in DMF for 15 min. The reagent was removed by filtration. The resin was successively washed with 3 x 20 mL DMF and 20 mL of a 1M solution of *N*-hydroxybenzotriazole in DMF. The resulting resin bound intermediate was treated with a solution of 4-bromomethylbenzoic acid (2.15 g, 10 mmol) and *N*-hydroxybenzotriazole (1.52 g, 10 mmol) in 25 mL THF

30

activated by diisopropylcarbodiimide (1.57 mL, 10 mmol). The reaction was performed at 25°C for 12 hours. Excess of reagents was removed by filtration. The resin bound intermediate was successively washed with 3 x 20 mL THF, 3 x 20 mL DMF and 3 x 20 mL methanol. The resin was dried in vacuo at 50°C for 16 hours to afford 3.77 g resin bound 3-[4-(bromo-methyl)benzoyl]aminopropionic acid.

An analytical sample of resin bound intermediate (0.05 g) was withdrawn and treated with 1 mL 50% TFA in dichloromethane for 30 min. The resin was drained and washed with dichloromethane several times. The combined filtrates were concentrated in vacuo. The residue was diluted with 20 mL of acetonitrile and characterized by analytical RP-HPLC ( $R_t$  = 8.25 min) and by HPLC-MS (Method A) ( $m/z$  = 287 ( $M + 1$ )).

Step C: Resin bound 3-(4-[(N-2,2-diphenylethyl)methyl]benzoyl)amino)propionic acid

The above resin bound 3-[4-(bromomethyl)benzoyl]aminopropionic acid (1.0 g, 0.64 mmol) was treated with 2,2-diphenylethylamine (1.26 g, 6.4 mmol) in 4 mL DMSO. The reaction was stirred at 80°C for 12 hours. Excess of reagents was removed by filtration. The resin was successively washed with 3 x 10 mL DMSO and 3 x 10 mL methanol and dried in vacuo at 50°C for 16 hours to afford 1.07 g resin bound 3-(4-[(N-2,2-diphenylethyl)methyl]benzoyl)amino)propionic acid.

An analytical sample of resin bound intermediate (0.05 g) was withdrawn and treated with 1 mL 50% TFA in dichloromethane for 30 min. The resin was drained and washed with dichloromethane several times. The combined filtrates were concentrated in vacuo. The residue was dissolved in 20 mL of acetonitrile and characterized by analytical RP-HPLC ( $R_t$  = 8.70 min) and by HPLC-MS (Method A) ( $m/z$  = 417 ( $M + 1$ )).

Step D: Resin bound 3-(4-[(N-(5-chlorobenzo[b]thiophen-3-carbonyl)-N-(2,2-diphenylethyl)amino)methyl]benzoyl)amino)propionic acid

The above resin bound 3-(4-[(N-2,2-diphenylethyl)methyl]benzoyl)amino)propionic acid (1.02 g, 0.61 mmol) was suspended in THF and successively washed with 2 x 10 mL THF, 2 x 10 mL 5% diisopropylethylamine in THF and 5 x 10 mL THF. The resin slurry was then treated with 5-chlorobenzo[b]thiophen-3-carboxylic acid (0.51 g, 2.4 mmol) in 4 mL THF, 4 mL pyridine, diisopropylcarbodiimide (0.19 mL, 1.2 mmol) and 4-dimethylaminopyridine (24 mg, 0.12 mmol). The reaction mixture was stirred at 25°C for 12 hours. The resin was drained and

successively washed with 3 x 10 mL THF, 3 x 10 mL DMF and 5 x 10 mL dichloromethane and used in next step without any characterization.

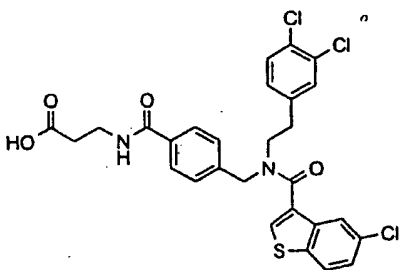
Step E: 3-(4-([N-(5-Chlorobenzo[b]thiophen-3-carbonyl)-N-(2,2-diphenylethyl)amino]methyl)-benzoylamino)propionic acid

The resin bound 3-(4-([N-(5-chlorobenzo[b]thiophen-3-carbonyl)-N-(2,2-diphenylethyl)-amino]methyl)benzoylamino)propionic acid was treated with a 50% solution of TFA in dichloromethane (10 mL). The cleavage mixture was stirred for 45 min at 25°C. The resin was drained and washed with dichloromethane several times. The combined filtrates were concentrated in vacuo. The residue was dissolved in a 1:1 mixture of methanol and dichloromethane (1 mL) and concentrated in vacuo to afford 0.359 g of the title compound. The product was characterized by analytical RP-HPLC ( $R_t$  = 14.2 min) and by HPLC-MS (Method A) ( $m/z$  = 597 ( $M + 1$ )).

The crude product (50 mg) was purified by column chromatography on RP-C18 silica gel (Sep-Pak, Waters) eluting with a mixture of acetonitrile and water. Pure fractions were pooled and evaporated in vacuo to afford 16.7 mg of pure title compound.

EXAMPLE 2 (general procedure (A))

3-(4-([N-(5-Chlorobenzo[b]thiophen-3-carbonyl)-N-(3,4-dichlorophenylethyl)amino]methyl)-benzoylamino)propionic acid

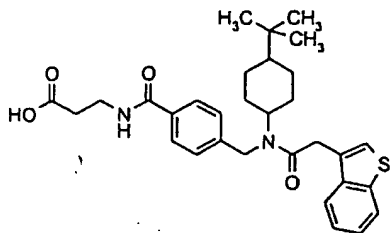


The product was characterized by analytical RP-HPLC ( $R_t$  = 14.12 min) and by HPLC-MS (Method A) ( $m/z$  = 589 ( $M + 1$ )).



EXAMPLE 3 (general procedure (A))

3-(4-([N-(2-Benzo[b]thiophen-3-yl-acetyl)-N-(4-*tert*-butylcyclohexyl)amino)methyl}benzoyl-amino)propionic acid

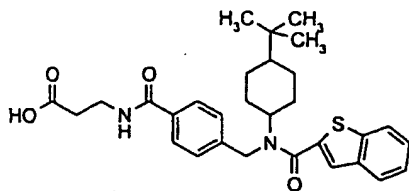


5

The product was characterized by analytical RP-HPLC ( $R_t = 14.96$  min) and by HPLC-MS (Method A) ( $m/z = 535$  ( $M + 1$ )).

EXAMPLE 4 (general procedure (A))

10 3-(4-([N-(Benzo[b]thiophen-2-carbonyl)-N-(4-*tert*-butylcyclohexyl)amino)methyl}benzoyl-amino)propionic acid



15

The product was characterized by analytical RP-HPLC ( $R_t = 15.17$  min) and by HPLC-MS (Method A) ( $m/z = 521$  ( $M + 1$ )).

EXAMPLE 5 (general procedure (A))

3-(4-([N-[3-(2,6-Dichlorophenyl)acryloyl]-N-(2-ethylhexyl)amino)methyl}benzoylamino)-propionic acid

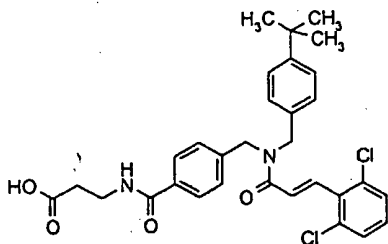


20

The product was characterized by analytical RP-HPLC ( $R_t = 15.26$  min) and by HPLC-MS (Method A) ( $m/z = 533$  ( $M + 1$ )).

EXAMPLE 6 (general procedure (A))

3-(4-([N-[3-(2,6-Dichlorophenyl)acryloyl]-N-(4-*tert*-butylbenzyl)amino]methyl)benzoylamino)-propionic acid

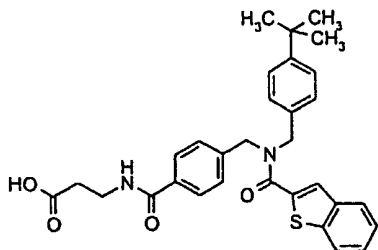


5

The product was characterized by analytical RP-HPLC ( $R_t = 15.08$  min) and by HPLC-MS (Method A) ( $m/z = 567$  ( $M + 1$ )).

EXAMPLE 7 (general procedure (A))

10 3-(4-([N-(Benzo[b]thiophen-2-carbonyl)-N-(4-*tert*-butylbenzyl)amino]methyl)benzoylamino)-propionic acid

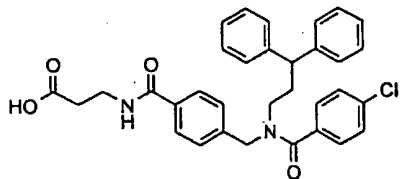


15

The product was characterized by analytical RP-HPLC ( $R_t = 14.70$  min) and by HPLC-MS (Method A) ( $m/z = 529$  ( $M + 1$ )).

EXAMPLE 8 (general procedure (A))

3-(4-([N-(4-Chlorobenzoyl)-N-(3,3-diphenylpropyl)amino]methyl)benzoylamino)propionic acid

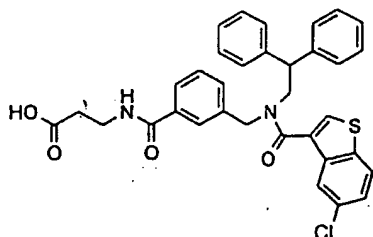


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The product was characterized by analytical RP-HPLC ( $R_t = 13.6$  min) and by HPLC-MS (Method A) ( $m/z = 555$  ( $M + 1$ )).

**EXAMPLE 9 (general procedure (A))**

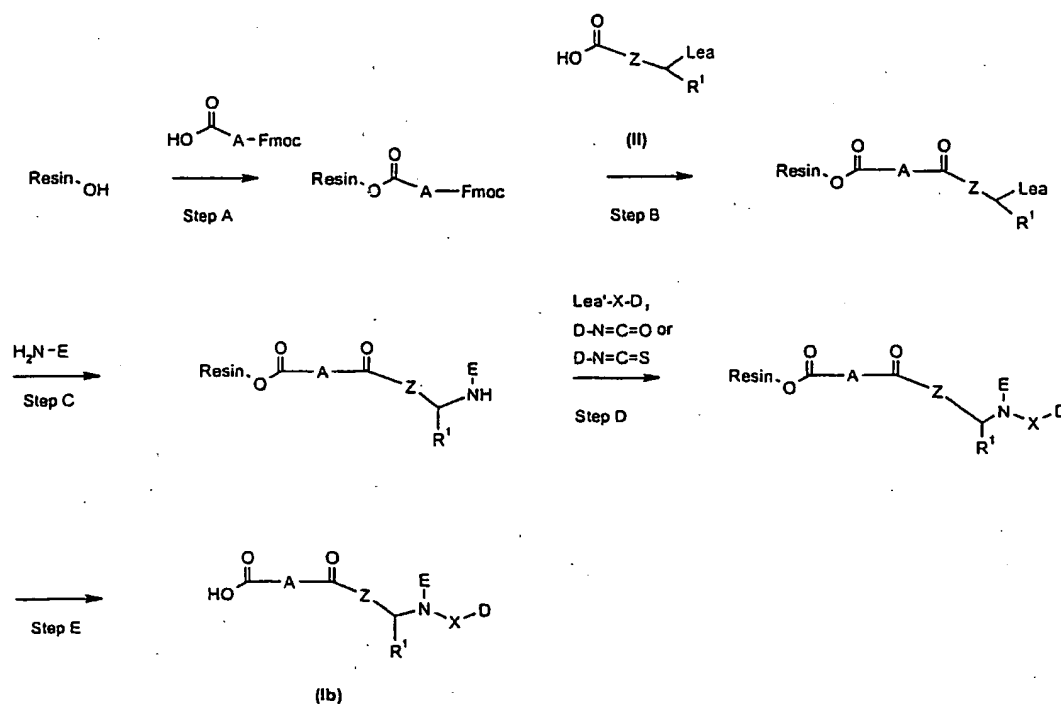
3-(3-([N-(5-Chlorobenzo[b]thiophene-3-carbonyl)-N-(2,2-diphenylethyl)amino]methyl)-benzoylamino)propionic acid



5

The product was characterized by analytical RP-HPLC ( $R_t = 14.5$  min) and by HPLC-MS (Method A) ( $m/z = 597$  ( $M + 1$ )).

- 10 General procedure (C) for the solid phase synthesis of compounds of the general formula (Ib):



wherein

15

A, Z,  $R^1$ , E and D are as defined for formula (I),

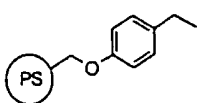
X is  $-S(O)_2-(CH_2)_r-$ ,  $-C(O)NH-$  or  $-C(S)NH-$ , wherein r is as defined for formula (I),

Lea is a leaving group such as chloro, bromo, iodo, mesyl or tosyl,

5

Lea' is a leaving group such as  $-OSu$ , chloro, phenoxy or 4-nitrophenoxy, and

Resin denotes a polystyrene resin with a linker such as the Wang linker:



10

wherein PS denotes polystyrene.

Step A:

15 Wang resin (10.0 g, Bachem 1250, 0.96 mmol/g) is suspended in NMP (100 mL) and drained, resuspended in THF (100 mL) and drained again. A solution of a Fmoc-protected amino acid (eg Fmoc- $\beta$ -alanine) (58 mmol), diisopropylcarbodiimide (4.2 g, 34 mmol) and 4-dimethylaminopyridine (0.07 g, 0.6 mmol) in THF (80 mL) is added to the resin and vortexed for 16 hours. The resin is drained and washed with THF (3 x 100 mL) and NMP (3 x 20 100 mL).

Step B:

All the resin synthesised in step A is used in this step. A solution of 20% piperidine in NMP (100 mL) is added to the resin and the mixture vortexed for 1 hour. After draining the resin is 25 washed in NMP (3 x 100 mL) and THF (5 x 100 mL). A solution of intermediate (II), eg 4-(bromomethyl)benzoic acid (or a substituted analogue thereof) (29 mmol), hydroxybenzotriazole (4.4 g, 29 mmol) and diisopropylcarbodiimide (3.6 g, 29 mmol) in THF (70 mL) is added and the mixture is vortexed for 16 hours. The resin is drained and washed with THF (2 x 100 mL), NMP (2 x 100 mL), dichloromethane (2 x 100 mL) and methanol (5 x 100 mL), 30 and dried in vacuo.

Step C:

6 g of the resin synthesised in step B is used in this step. A solution of a primary amine (eg 2-phenethylamine or 4-*tert*-butylcyclohexylamine) (48 mmol) in DMSO is added to the resin

and vortexed at 80°C for 16 hours. The resin is drained and washed with NMP (3 x 100 mL), dichloromethane (3 x 100 mL) and methanol (4 x 100 mL), and dried in vacuo.

Step D:

- 5 50 mg of the resin produced in step C is used in this step. The resin is suspended in NMP (1.5 mL) and drained. A solution of an isothiocyanate or an isocyanate (eg phenylisocyanate or 4-trifluoromethoxyphenylisocyanate) (0.24 mmol) in NMP (1 mL) is added and the mixture is vortexed for 16 hours. Alternatively, a solution of Lea'-X-D in an appropriate solvent such as acetonitrile, toluene, DMF, NMP, THF, dichloromethane, 1,2-dichloroethane or DMSO or
- 10 a mixture of two or more of these, is added and the mixture is vortexed in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine or potassium carbonate under heating, if necessary. The resin is drained and washed with DMF (3 x 1 mL), methanol (3 x 1 mL), 2-propanol (3 x 1 mL), *tert*-butyl-methylether (3 x 1 mL) and dichloromethane (3 x 1 mL).

15

Step E:

All the resin synthesised in step D is used. A solution of TFA and dichloromethane (1:1, 2 mL) is added to the resin and vortexed for 45 min. The resin is drained and the eluent evaporated in vacuo to give a compound of general formula (Ib).

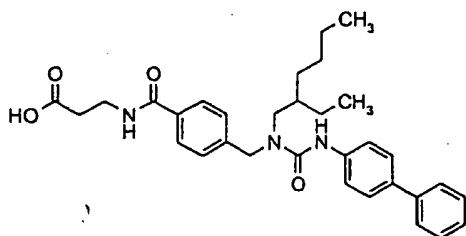
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Optionally, the compound can be purified by chromatography eg HPLC.

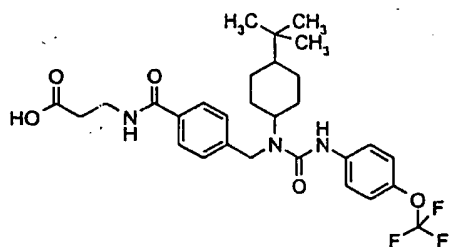
- The compounds of general formula (Ib) can be prepared either as single compounds or by parallel synthesis using the protocol mentioned above in a combinatorial approach. Thousands of
- 25 compounds of formula (Ib) can thus be prepared by this combinatorial approach which can be semi-automated or fully automated. The automation of this protocol can be performed eg using a 96 well setup using an automated synthesizer device.

30

The following examples were prepared according to general procedure (C).

EXAMPLE 10 (general procedure (C))3-{4-[3-Biphenyl-4-yl-1-(2-ethylhexyl)ureidomethyl]benzoylamino}propionic acid

- 5 The product was characterized by HPLC-MS (Method C):  $R_t = 4.30$  min,  $m/z = 530$  ( $M + 1$ ).

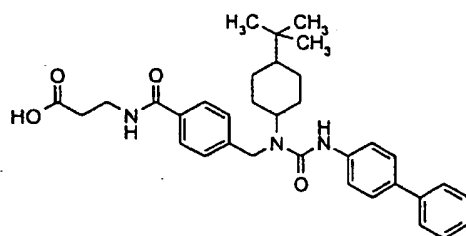
EXAMPLE 11 (general procedure (C))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

10

The product was characterized by HPLC-MS (Method C):  $R_t = 4.33$  min,  $m/z = 564$  ( $M + 1$ ).

EXAMPLE 12 (general procedure (C))

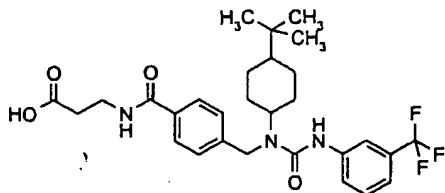
- 15 3-{4-[3-Biphenyl-4-yl-1-(4-*tert*-butylcyclohexyl)ureidomethyl]benzoylamino}propionic acid



The product was characterized by HPLC-MS (Method C):  $R_t = 4.40$  min,  $m/z = 556$  ( $M + 1$ ).

EXAMPLE 13 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-trifluoromethylphenyl)ureidomethyl]benzoylamino}-propionic acid

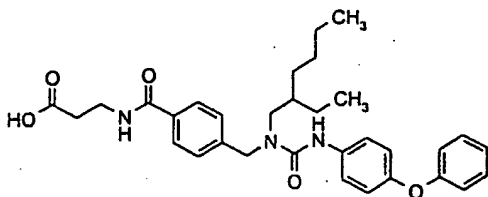


5

The product was characterized by HPLC-MS (Method C):  $R_t = 4.31$  min,  $m/z = 548$  ( $M + 1$ ).

EXAMPLE 14 (general procedure (C))

3-{4-[1-(2-Ethylhexyl)-3-(4-phenoxyphenyl)ureidomethyl]benzoylamino}propionic acid

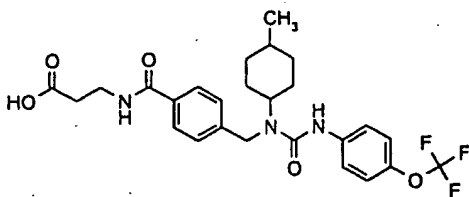


10

The product was characterized by HPLC-MS (Method C):  $R_t = 4.30$  min,  $m/z = 546$  ( $M + 1$ ).

EXAMPLE 15 (general procedure (C))

15 3-{4-[1-(4-Methylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

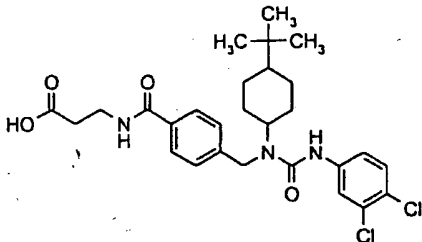


20

The product was characterized by HPLC-MS (Method C):  $R_t = 3.78$  min,  $m/z = 522$  ( $M + 1$ ).

EXAMPLE 16 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,4-dichlorophenyl)ureidomethyl]benzoylamino}propionic acid



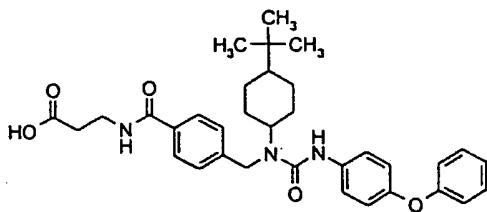
5

The product was characterized by HPLC-MS (Method C):  $R_t = 4.62$  min,  $m/z = 548$  ( $M + 1$ ).

EXAMPLE 17 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-phenoxyphenyl)ureidomethyl]benzoylamino}propionic acid

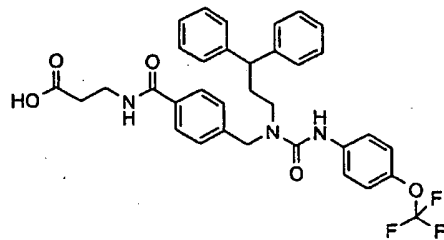
10



The product was characterized by HPLC-MS (Method C):  $R_t = 4.30$  min,  $m/z = 572$  ( $M + 1$ ).

EXAMPLE 18 (general procedure (C))

3-{4-[1-(3,3-Diphenylpropyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



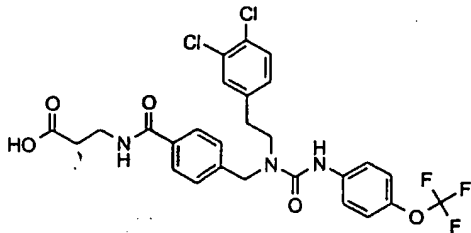
20

The product was characterized by HPLC-MS (Method C):  $R_t = 4.13$  min,  $m/z = 620$  ( $M + 1$ ).



EXAMPLE 19 (general procedure (C))

3-{4-[1-[2-(3,4-Dichlorophenyl)ethyl]-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl-amino}propionic acid

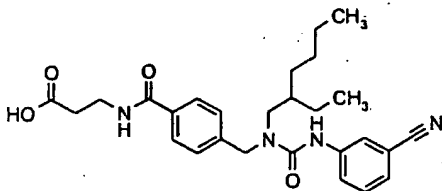


5

The product was characterized by HPLC-MS (Method C):  $R_t = 4.00$  min,  $m/z = 598$  ( $M + 1$ ).

EXAMPLE 20 (general procedure (C))

3-{4-[3-(3-Cyanophenyl)-1-(2-ethylhexyl)ureidomethyl]benzoylamino}propionic acid

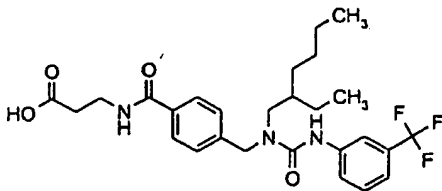


10

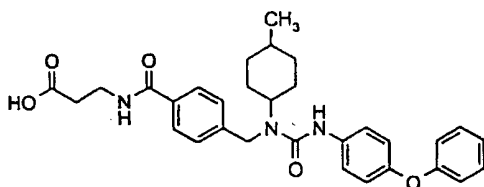
The product was characterized by HPLC-MS (Method B):  $R_t = 5.50$  min,  $m/z = 479$  ( $M + 1$ ).

EXAMPLE 21 (general procedure (C))

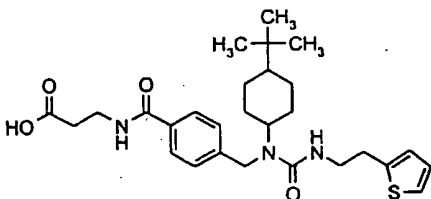
15 3-{4-[1-(2-Ethylhexyl)-3-(3-trifluoromethylphenyl)ureidomethyl]benzoylamino}propionic acid



The product was characterized by HPLC-MS (Method B):  $R_t = 6.17$  min,  $m/z = 552$  ( $M + 1$ ).

EXAMPLE 22 (general procedure (C))3-{4-[1-(4-Methylcyclohexyl)-3-(4-phenoxyphenyl)ureidomethyl]benzoylamino}propionic acid

- 5 The product was characterized by HPLC-MS (Method B):  $R_t = 5.73$  min,  $m/z = 530$  ( $M + 1$ ).

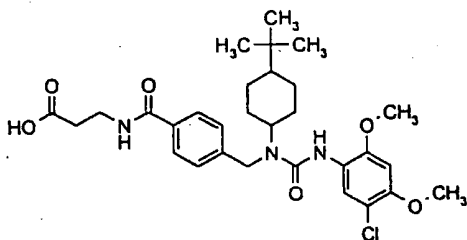
EXAMPLE 23 (general procedure (C))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(2-thiophen-2-ylethyl)ureidomethyl]benzoylamino}propionic acid

10

The product was characterized by HPLC-MS (Method B):  $R_t = 5.60$  min,  $m/z = 514$  ( $M + 1$ ).

EXAMPLE 24 (general procedure (C))

- 15 3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(5-chloro-2,4-dimethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

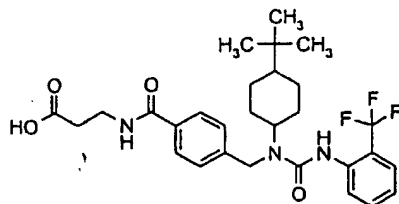


The product was characterized by HPLC-MS (Method B):  $R_t = 6.30$  min,  $m/z = 574$  ( $M + 1$ ).

20

EXAMPLE 25 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(2-trifluoromethylphenyl)ureidomethyl]benzoylamino}-propionic acid



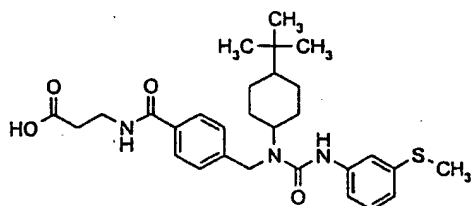
5

The product was characterized by HPLC-MS (Method B):  $R_t = 6.10$  min,  $m/z = 548$  ( $M + 1$ ).

EXAMPLE 26 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-methylsulfanylphenyl)ureidomethyl]benzoylamino}-propionic acid

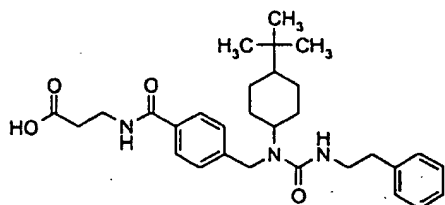
10



The product was characterized by HPLC-MS (Method B):  $R_t = 6.03$  min,  $m/z = 526$  ( $M + 1$ ).

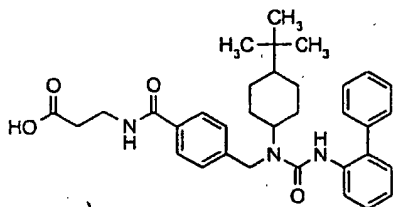
EXAMPLE 27 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-phenethylureidomethyl]benzoylamino}propionic acid

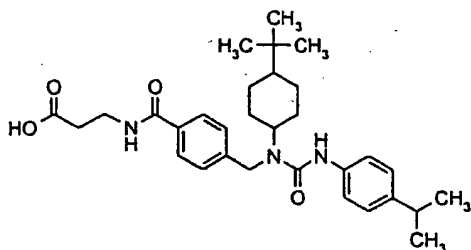


The product was characterized by HPLC-MS (Method B):  $R_t = 5.53$  min,  $m/z = 508$  ( $M + 1$ ).

20

EXAMPLE 28 (general procedure (C))3-{4-[3-Biphenyl-2-yl-1-(4-*tert*-butylcyclohexyl)ureidomethyl]benzoylamino}propionic acid

- 5 The product was characterized by HPLC-MS (Method B):  $R_t = 6.14$  min,  $m/z = 556$  ( $M + 1$ ).

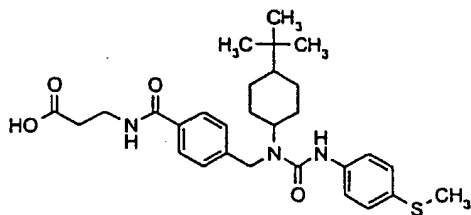
EXAMPLE 29 (general procedure (C))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-isopropylphenyl)ureidomethyl]benzoyl}aminopropionic acid

10

The product was characterized by HPLC-MS (Method B):  $R_t = 7.98$  min,  $m/z = 522$  ( $M+1$ ).

EXAMPLE 30 (general procedure (C))

- 15 3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-methylsulfanylphenyl)ureidomethyl]benzoyl}amino-propionic acid

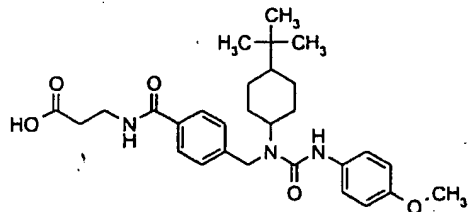


The product was characterized by HPLC-MS (Method B):  $R_t = 7.58$  min,  $m/z = 526$  ( $M+1$ ).

20

EXAMPLE 31 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-methoxyphenyl)ureidomethyl]benzoyl}aminopropionic acid

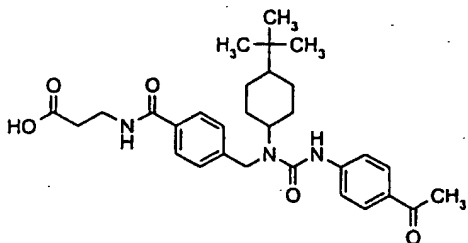


5

The product was characterized by HPLC-MS (Method B):  $R_t = 6.93$  min,  $m/z = 510$  (M+1).

EXAMPLE 32 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-acetylphenyl)ureidomethyl]benzoyl}aminopropionic acid

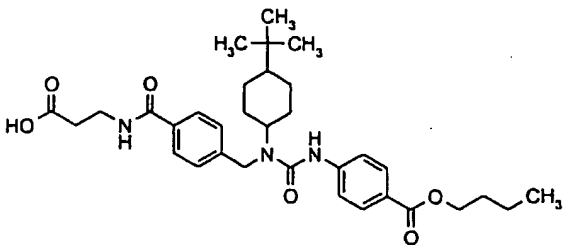


10

The product was characterized by HPLC-MS (Method B):  $R_t = 7.03$  min,  $m/z = 522$  (M+1).

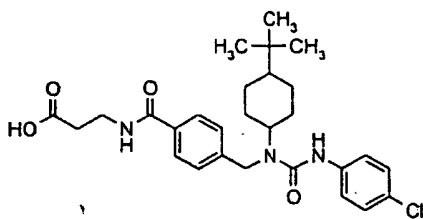
EXAMPLE 33 (general procedure (C))

4-{3-[4-(4-*tert*-Butylcyclohexyl)-3-(4-(2-carboxyethylcarbamoyl)benzyl)ureido]benzoic acid butyl ester

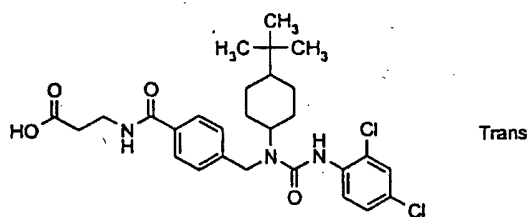


20

The product was characterized by HPLC-MS (Method B):  $R_t = 8.33$  min.

**EXAMPLE 34 (general procedure (C))****3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]benzoyl}aminopropionic acid**

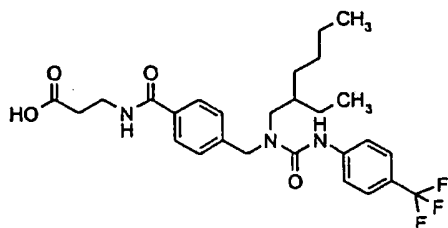
- 5 The product was characterized by HPLC-MS (Method B):  $R_t = 7.68$  min,  $m/z = 514$  ( $M+1$ ).

**EXAMPLE 35 (general procedure (C))****3-{4-[1-(4-*trans-tert*-Butylcyclohexyl)-3-(2,4-dichlorophenyl)ureidomethyl]benzoylamino}-propionic acid**

10

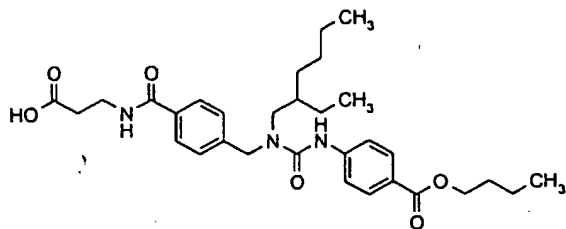
$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  0.82 (9H, s), 0.9-1.7 (9H, m), 4.04 (1H, t), 4.60 (2H, s), 7.38 (4H, m), 7.60 (2H, m), 7.78 (2H, d), 8.48 (1H, t).

- 15 HPLC-MS (Method B):  $R_t = 8.25$  min,  $m/z = 548$  ( $M+1$ ).

**EXAMPLE 36 (general procedure (C))****3-{4-[1-(2-Ethylhexyl)-3-(4-trifluoromethylphenyl)ureidomethyl]benzoylamino}propionic acid**

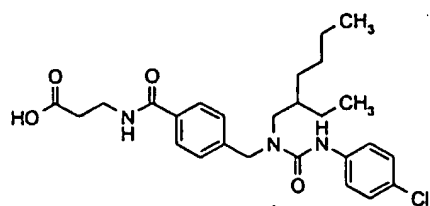
20

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  7.33 (2H, d), 7.59 (2H, d), 7.68 (2H, d), 7.81 (2H, d), 8.50 (1H, t), 8.81 (1H, s).

EXAMPLE 37 (general procedure (C))4-[3-[4-(2-Carboxyethylcarbamoyl)benzyl]-3-(2-ethylhexyl)ureido]benzoic acid butyl ester

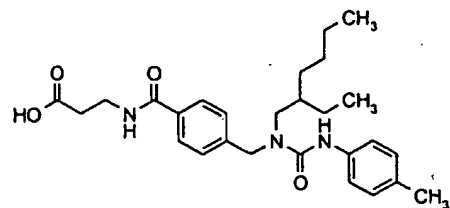
5

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  4.23 (2H, t), 4.69 (2H, s), 7.33 (2H, d), 7.60 (2H, d), 7.80 (2H, d), 7.84 (2H, d), 8.49 (1H, bt), 8.81 (1H, s).

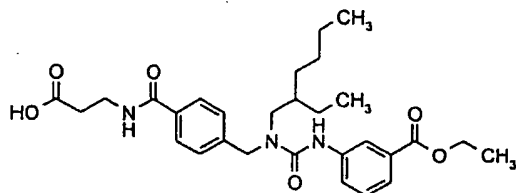
EXAMPLE 38 (general procedure (C))10 3-[4-[3-(4-Chlorophenyl)-1-(2-ethylhexyl)ureidomethyl]benzoylamino]propionic acid

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  4.64 (2H, s), 7.04 (2H, d), 7.3-7.35 (4H, m), 7.81 (2H, d), 8.28 (1H, s), 8.48 (1H, bt).

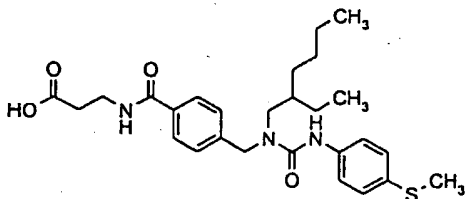
15

EXAMPLE 39 (general procedure (C))3-[4-[1-(2-Ethylhexyl)-3-p-tolylureidomethyl]benzoylamino]propionic acid

20  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  4.65 (2H, s), 7.06 (2H, d), 7.31-7.33 (4H, m), 7.81 (2H, d), 8.29 (1H, s), 8.49 (1H, bt).

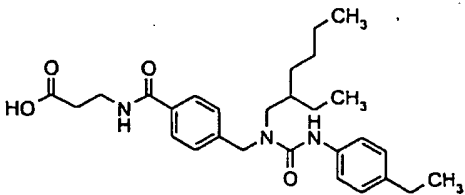
EXAMPLE 40 (general procedure (C))3-[3-[4-(2-Carboxyethylcarbamoyl)benzyl]-3-(2-ethylhexyl)ureido]benzoic acid ethyl ester

- 5  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  4.30 (2H, q), 4.67 (2H, s), 7.33 (2H, d), 7.36 (1H, t), 7.53 (1H, t), 7.74 (1H, bd), 7.80 (2H, d), 8.07 (1H, s), 8.48 (1H, bt), 8.65 (1H, s).

EXAMPLE 41 (general procedure (C))3-[4-[1-(2-Ethylhexyl)-3-(4-methylsulfanylphenyl)ureidomethyl]benzoylamino]propionic acid

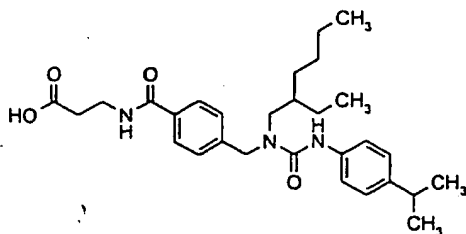
10

- $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  4.66 (2H, s), 7.18 (2H, d), 7.31 (2H, d), 7.39 (2H, d), 7.78 (2H, d), 8.40 (1H, s), 8.50 (1H, bt).

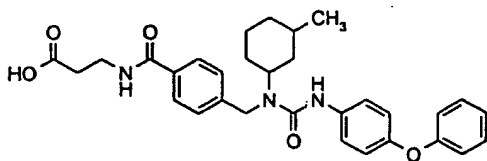
15 EXAMPLE 42 (general procedure (C))3-[4-[1-(2-Ethylhexyl)-3-(4-ethylphenyl)ureidomethyl]benzoylamino]propionic acid

- 20  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  4.51 (2H, s), 7.10 (2H, d), 7.32 (4H, m), 7.79 (2H, d), 8.28 (1H, s), 8.48 (1H, t).



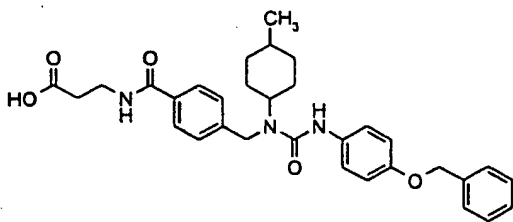
EXAMPLE 43 (general procedure (C))3-{4-[1-(2-Ethylhexyl)-3-(4-isopropylphenyl)ureidomethyl]benzoylamino}propionic acid

- 5  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  4.70 (2H, s), 7.33 (2H, d), 7.58 (2H, d), 7.67 (2H, d), 7.78 (2H, d), 8.46 (1H, t), 8.70 (1H, d).

EXAMPLE 44 (general procedure (C))3-{4-[1-(3-Methylcyclohexyl)-3-(4-phenoxyphenyl)ureidomethyl]benzoylamino}propionic acid

10

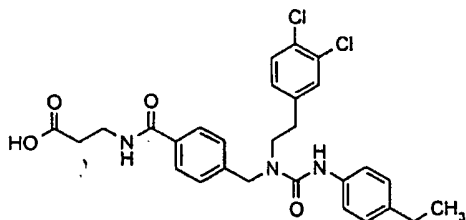
- $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  4.61 (2H, s), 6.92 (4H, m), 7.07 (1H, t), 7.33 (4H, m), 7.41 (2H, m), 7.76 (2H, d), 8.29 (1H, d), 8.45 (1H, t).

EXAMPLE 45 (general procedure (C))3-{4-[3-(4-Benzoyloxyphenyl)-1-(4-methylcyclohexyl)ureidomethyl]benzoylamino}propionic acid

- 20  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  5.01 (2H, s), 6.90 (2H, d), 7.1-7.3 (10H, m), 7.77 (2H, d), 8.15 (1H, s), 8.44 (1H, bt).

**EXAMPLE 46 (general procedure (C))**

3-{4-[1-[2-(3,4-Dichlorophenyl)ethyl]-3-(4-ethylphenyl)ureidomethyl]benzoylamino}propionic acid

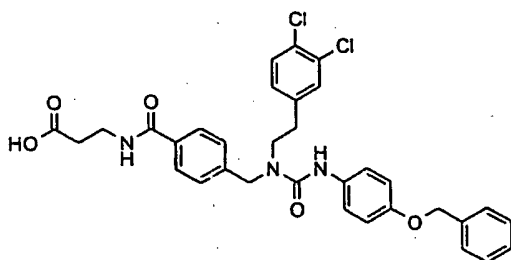


5

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  4.67 (2H, s), 7.08 (2H, d), 7.25 (1H, d), 7.35 (4H, m), 7.53 (2H, m), 7.81 (2H, d), 8.31 (1H, s), 8.48 (1H, bt).

**EXAMPLE 47 (general procedure (C))**

10 3-{4-[3-(4-Benzyloxyphenyl)-1-[2-(3,4-dichlorophenyl)ethyl]ureidomethyl]benzoylamino}-propionic acid

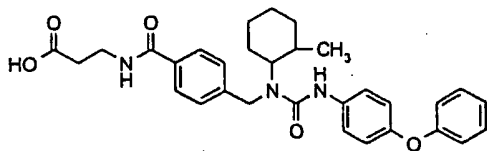


15

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  4.60 (2H, s), 5.10 (2H, s), 6.92 (2H, d), 7.25-7.47 (10H, m), 7.55 (2H, m), 7.25 (1H, d), 7.81 (2H, d), 8.27 (1H, s), 8.45 (1H, t).

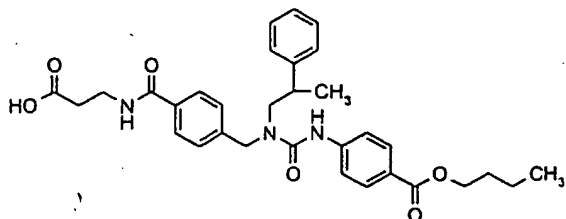
**EXAMPLE 48 (general procedure (C))**

3-{4-[1-(2-Methylcyclohexyl)-3-(4-phenoxyphenyl)ureidomethyl]benzoylamino}propionic acid

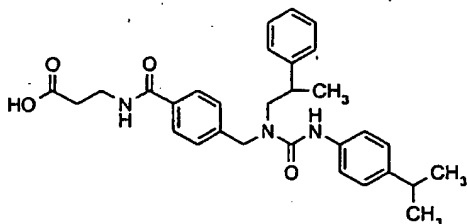


20

HPLC-MS (Method C):  $m/z$ : 530,  $R_t$  = 6.96 min.

EXAMPLE 49 (general procedure (C))4-[3-[4-(2-Carboxyethylcarbamoyl)benzyl]-3-(2-phenylpropyl)ureido]benzoic acid butyl ester

- 5  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  7.20 (2H, t), 7.3 (6H, m), 7.55 (2H, d), 7.77 (2H, d), 7.83 (2H, d), 8.46 (1H, d), 8.69 (1H, s).

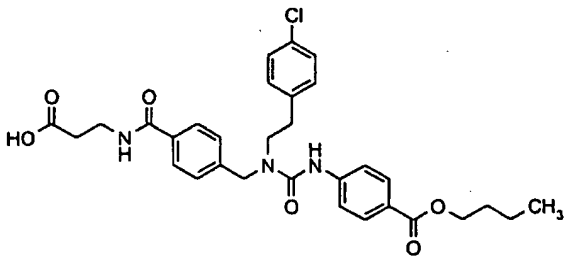
EXAMPLE 50 (general procedure (C))3-[4-[3-(4-Isopropylphenyl)-1-(2-phenylpropyl)ureidomethyl]benzoylamino]propionic acid

10

- $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  7.11 (2H, d), 7.2-7.35 (9H, m), 7.78 (2H, d), 8.23 (1H, s), 8.49 (1H, t).

EXAMPLE 51 (general procedure (C))

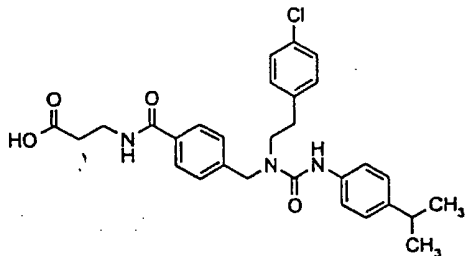
- 15 4-[3-[4-(2-Carboxyethylcarbamoyl)benzyl]-3-[2-(4-chlorophenyl)ethyl]ureido]benzoic acid butyl ester



- 20  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  7.27 (2H, d), 7.31-7.36 (4H, m), 7.60 (2H, d), 7.81 (2H, d), 7.86 (2H, d), 8.47 (1H, t), 8.77 (1H, s).

EXAMPLE 52 (general procedure (C))

3-{4-[1-[2-(4-Chlorophenyl)ethyl]-3-(4-isopropylphenyl)ureidomethyl]benzoylamino}propionic acid

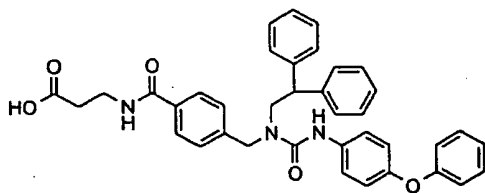


5

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  7.10 (2H, d), 7.24 (2H, d), 7.30-7.34 (6H, m), 7.78 (2H, d), 8.29 (1H, s).

EXAMPLE 53 (general procedure (C))

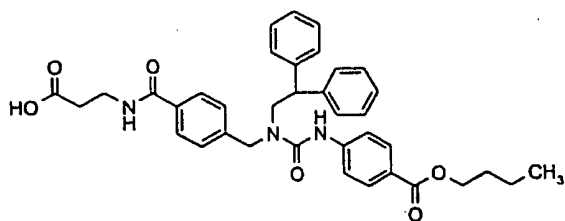
10 3-{4-[1-(2,2-Diphenylethyl)-3-(4-phenoxyphenyl)ureidomethyl]benzoylamino}propionic acid



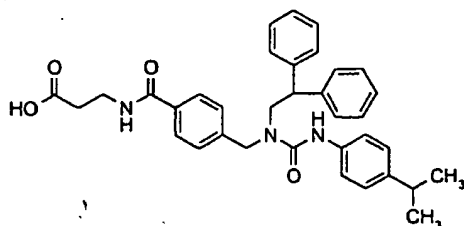
HPLC-MS (Method C):  $m/z$  614,  $R_t$  = 7.35 min.

15 EXAMPLE 54 (general procedure (C))

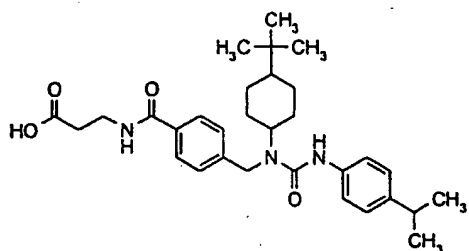
4-[3-[4-(2-Carboxyethylcarbamoyl)benzyl]-3-(2,2-diphenylethyl)ureido]benzoic acid butyl ester



20  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  7.18 (2H, t), 7.25-7.3 (6H, m), 7.34 (4H, m), 7.47 (2H, d), 7.75 (2H, d), 7.80 (2H, d), 8.52 (1H, b), 8.71 (1H, s).

EXAMPLE 55 (general procedure (C))3-{4-[1-(2,2-Diphenylethyl)-3-(4-isopropylphenyl)ureidomethyl]benzoylamino}propionic acid

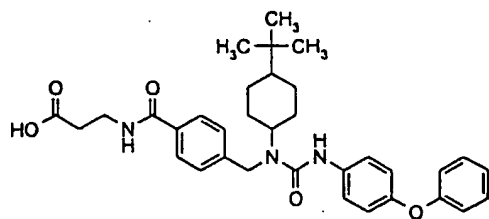
5 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 7.06 (2H, d), 7.16-7.35 (14H, m), 7.75 (2H, d), 8.24 (1H, s).

EXAMPLE 56 (general procedure (C))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-isopropylphenyl)ureidomethyl]benzoylamino}propionic acid

10

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.41 (s, 1H); 8.20 (s, 1H); 7.75 (d, 2H); 7.34 (d, 2H); 7.32 (d, 2H); 7.08 (d, 2H); 4.08 (s, 2H); 1.19 (d, 6H); 0.83 (s, 9H).

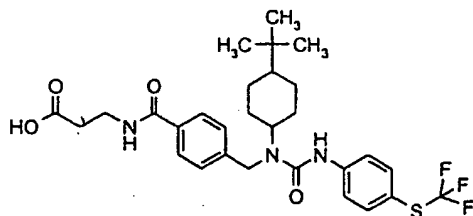
15 EXAMPLE 57 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-phenoxyphenyl)ureidomethyl]benzoylamino}propionic acid

20 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.44 (s, 1H); 8.35 (s, 1H); 7.78 (d, 2H); 7.45 (d, 2H); 7.38 (d, 2H); 7.34 (d, 2H); 6.94 (m, 5H); 4.60 (s, 2H); 0.81 (s, 9H).

EXAMPLE 58 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]-benzoylamino}propionic acid

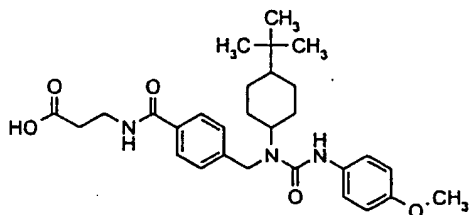


5

$^1\text{H NMR}$  (DMSO- $d_6$ ):  $\delta$  8.46 (s, 1H); 8.34 (s, 1H); 7.74 (d, 2H); 7.40 (d, 2H); 7.34 (d, 2H); 7.16 (d, 2H); 4.59 (s, 2H); 0.85 (s, 9H).

10 EXAMPLE 59 (general procedure (C))

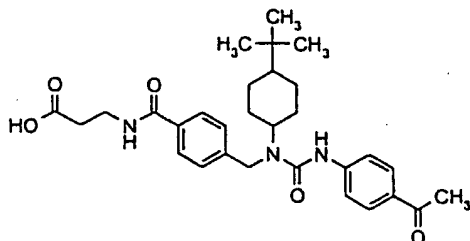
3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-methoxyphenyl)ureidomethyl]benzoylamino}propionic acid



15  $^1\text{H NMR}$  (DMSO- $d_6$ ):  $\delta$  8.46 (s, 1H); 8.18 (s, 1H); 7.76 (d, 2H); 7.30 (d, 2H); 7.28 (d, 2H); 6.8 (d, 2H); 4.58 (s, 2H); 3.73 (s, 3H); 0.80 (s, 9H).

EXAMPLE 60 (general procedure (C))

3-{4-[3-(4-Acetylphenyl)-1-(4-*tert*-butylcyclohexyl)ureidomethyl]benzoylamino}propionic acid

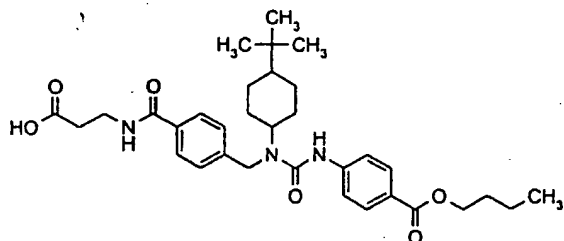


20

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.70 (s, 1H); 8.42 (s, 1H); 7.86 (d, 2H); 7.76 (d, 2H); 7.62 (d, 2H); 7.30 (d, 2H); 4.62 (s, 2H); 0.81 (s, 9H).

**EXAMPLE 61 (general procedure (C))**

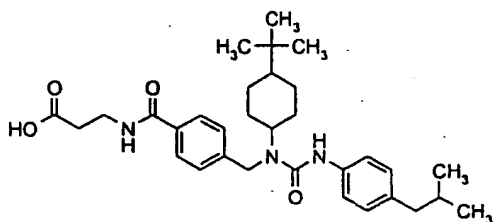
5 4-{3-(4-*tert*-Butylcyclohexyl)-3-[4-(2-carboxyethylcarbamoyl)benzyl]ureido}benzoic acid butyl ester



10 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.71 (s, 1H); 8.42 (t, 1H); 7.83 (d, 2H); 7.76 (d, 2H); 7.61 (s, 2H); 7.32 (d, 2H); 4.64 (s, 2H); 4.26 (t, 2H); 0.94 (t, 3H); 0.83 (s, 9H).

**EXAMPLE 62 (general procedure (C))**

3-[4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-isobutylphenyl)ureidomethyl]benzoylamino}propionic acid

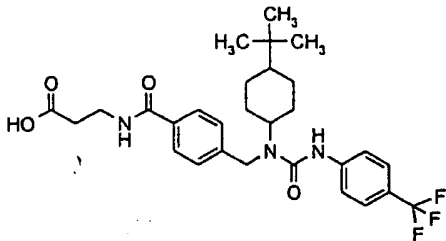


15

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.46 (t, 1H); 8.22 (s, 1H); 7.75 (d, 2H); 7.35 (d, 2H); 7.33 (d, 2H); 7.05 (d, 2H); 4.60 (s, 2H); 1.17 (d, 6H); 0.83 (s, 9H).

**EXAMPLE 63 (general procedure (C))**

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethylphenyl)ureidomethyl]benzoylamino}-propionic acid

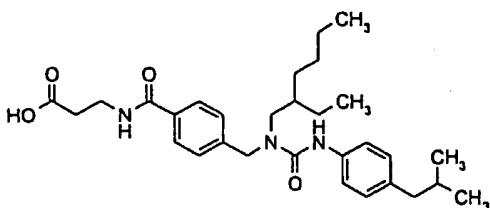


5

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  8.72 (s, 1H); 8.45 (t, 1H); 7.78 (d, 2H); 7.72 (d, 2H); 7.60 (d, 2H); 7.35 (d, 2H); 4.65 (s, 2H); 4.10 (m, 1H); 0.85 (s, 9H).

**EXAMPLE 64 (general procedure (C))**

10 3-{4-[1-(2-Ethylhexyl)-3-(4-isobutylphenyl)ureidomethyl]benzoylamino}propionic acid

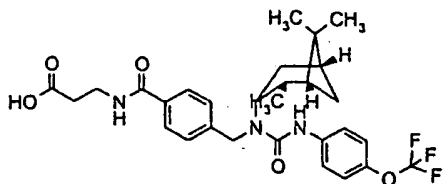


$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  8.47 (t, 1H); 8.30 (s, 1H); 7.82 (d, 2H); 7.36 (d, 2H); 7.32 (d, 2H); 7.05 (d, 2H); 4.65 (s, 2H); 1.12 (m, 9H); 0.85 (m, 12H).

15

**EXAMPLE 65 (general procedure (C))**

3-{4-[3-(4-Trifluoromethoxyphenyl)-1-(2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)ureidomethyl]benzoylamino}propionic acid



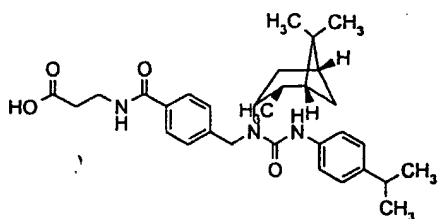
20

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  8.52 (s, 1H); 8.44 (t, 1H); 7.81 (d, 2H); 7.52 (d, 2H); 7.35 (d, 2H); 7.22 (d, 2H); 4.91 (m, 1H); 4.76 (s, 2H); 1.22 (s, 3H); 1.13 (s, 3H); 0.98 (d, 3H).



**EXAMPLE 66 (general procedure (C))**

3-[4-[3-(4-Isopropylphenyl)-1-(2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)ureidomethyl]benzoyl-amino}propionic acid

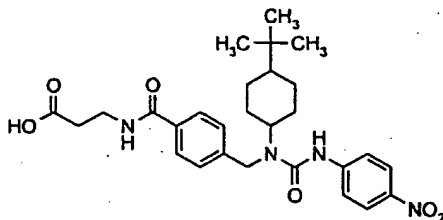


5

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  8.44 (s, 1H); 8.17 (t, 1H); 7.78 (d, 2H); 7.34 (d, 2H); 7.26 (d, 2H); 7.08 (d, 2H); 4.93 (m, 1H); 4.72 (s, 2H); 1.22 (s, 3H); 1.18 (d, 6H); 1.13 (s, 3H); 0.98 (d, 3H).

**EXAMPLE 67 (general procedure (C))**

10 3-[4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-nitrophenyl)ureidomethyl]benzoylamino}propionic acid

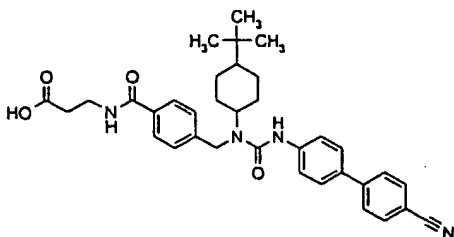


$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  9.03 (s, 1H); 8.45 (t, 1H); 8.16 (d, 2H); 7.77 (d, 2H); 7.73 (d, 2H); 7.33 (d, 2H); 4.67 (s, 2H); 4.10 (t, 1H); 0.86 (s, 9H).

15

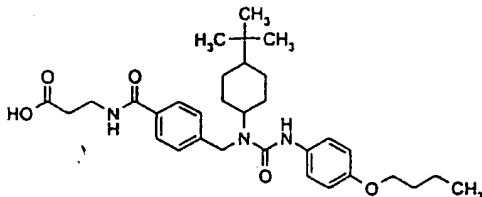
**EXAMPLE 68 (general procedure (C))**

3-[4-[1-(4-*tert*-Butylcyclohexyl)-3-(4'-cyanobiphenyl-4-yl)ureidomethyl]benzoylamino}-propionic acid



20

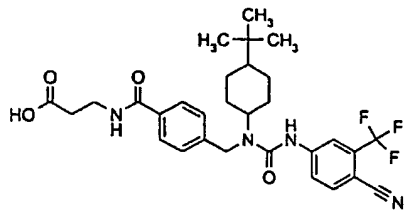
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  8.52 (1H, s), 8.48 (1H, t), 7.88 (4H, dd), 7.79 (2H, d), 7.79 (2H, d), 7.62 (2H, d), 7.38 (2H, d).

EXAMPLE 69 (general procedure (C))3-{4-[3-(4-Butoxyphenyl)-1-(4-*tert*-butyl-cyclohexyl)ureidomethyl]benzoylamino}propionic acid

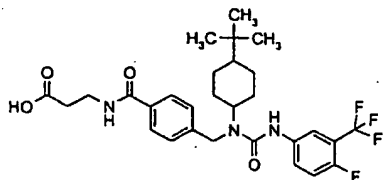
5

 $^1\text{H NMR}$  (DMSO- $d_6$ ):  $\delta$  8.45 (1H, m), 8.15 (1H, s), 7.78 (2H, d), 7.33 (4H, dd), 6.82 (2H, d).EXAMPLE 70 (general procedure (C))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-cyano-3-trifluoromethylphenyl)ureidomethyl]benzoyl-  
amino}propionic acid

10

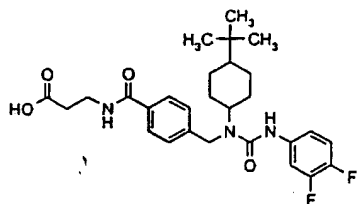
 $^1\text{H NMR}$  (DMSO- $d_6$ ):  $\delta$  8.43 (1H, m), 8.18 (1H, s), 7.98 (2H, s), 7.75 (2H, d), 7.43 (2H, d).

15

EXAMPLE 71 (general procedure (C))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-fluoro-3-trifluoromethylphenyl)ureidomethyl]benzoyl-  
amino}propionic acid20 HPLC-MS (method B):  $m/z$ : 566,  $R_t$  = 7.95 min.

EXAMPLE 72 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,4-difluorophenyl)ureidomethyl]benzoylamino}propionic acid

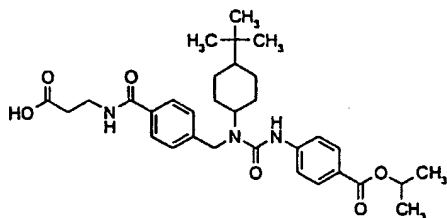


5

HPLC-MS (method B):  $m/z$ : 517,  $R_t$  = 7.29 min.

EXAMPLE 73 (general procedure (C))

4-{3-(4-*tert*-Butylcyclohexyl)-3-[4-(2-carboxyethylcarbamoyl)benzyl]ureido}benzoic acid isopropyl ester



10

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  8.70 (1H, s), 8.48 (1H, t), 7.83 (2H, d), 7.78 (2H, d), 7.63 (2H, d), 7.32 (2H, d).

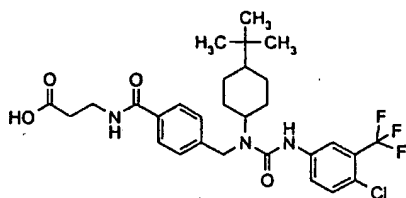
15

HPLC-MS (method B):  $m/z$ : 566,  $R_t$  = 7.69 min.

EXAMPLE 74 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]benzoylamino}propionic acid

20



$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  8.80 (1H, s), 8.48 (1H, t), 8.05 (1H, s), 7.82 (1H, d), 7.77 (1H, d), 7.58 (1H, d), 7.32 (1H, s).

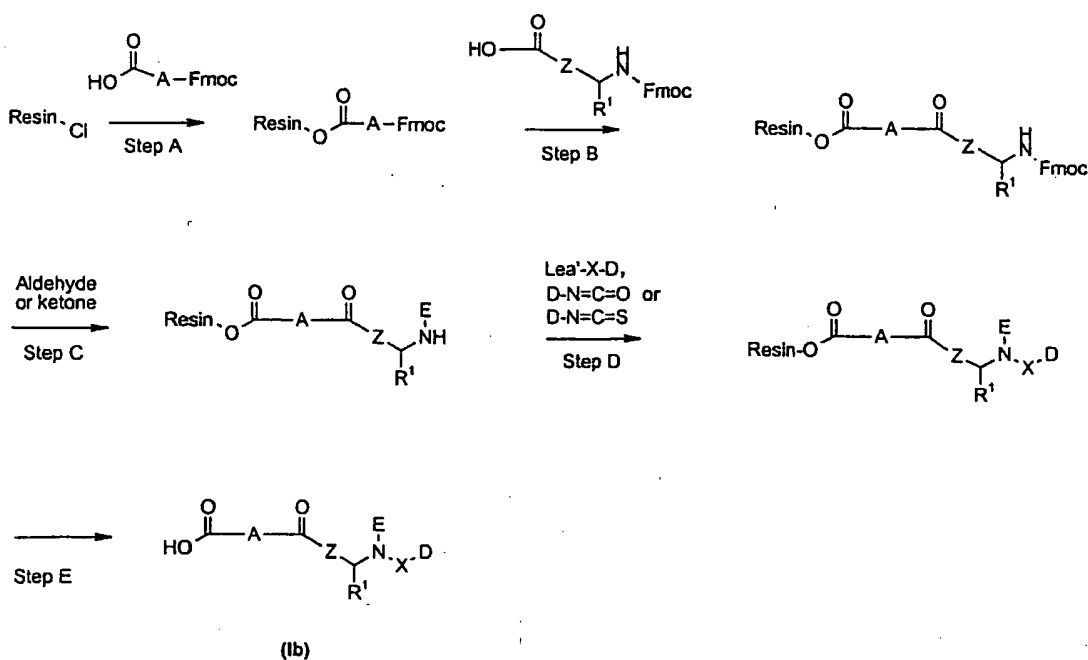
HPLC-MS (method B):  $m/z$ : 583,  $R_t$  = 8.03 min.

5

General procedure (D) for the solid phase synthesis of compounds of the general formula (Ib):

The compounds of the general formula (Ib) may also be prepared by the use of the following method:

10

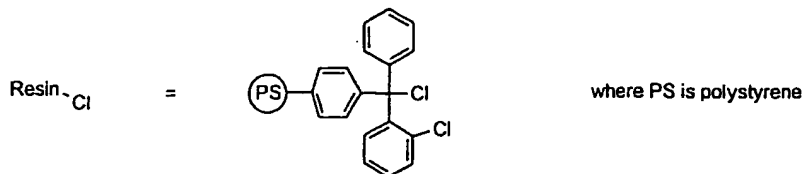


wherein

15  $R^1$ , A, Z, E and D are as defined for formula (I),

X is  $-\text{S(O)}_2-(\text{CH}_2)_r-$ ,  $-\text{C(O)NH-}$  or  $-\text{C(S)NH-}$ , wherein r is as defined for formula (I),

Lea' represents a leaving group such as  $-\text{OSu}$ ,  $\text{Cl-}$ ,  $\text{PhO-}$ , or  $4\text{-NO}_2\text{-PhO-}$ , and

Step A:

The reaction is known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 24) and is generally performed by shaking a suspension of the resin with a solution of an Fmoc amino acid in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine. Typical solvents are pyridine, dichloromethane, 1,2-dichloroethane, DMF, NMP, THF, DMSO or mixtures of two or more of these. The reaction is performed between 20°C and 120°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed with any solvent mentioned above including mixtures hereof, containing a base as mentioned above and an alcohol, typically methanol, as a scavenger of unreacted resin bound 2-chlorotritylchloride.

Step B:

The Fmoc protecting group is removed using a solution of 20% piperidine in DMF, which is added to the resin and vortexed for 0.5 hours. After draining the resin is washed with DMF containing 1-hydroxybenzotriazole (50 mg/mL) and DMF.

The acylation (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 78) is performed by adding an excess of Fmoc amino-benzoic acid in a solvent such as DMF, NMP, THF, dichloromethane, 1,2-dichloroethane, acetonitrile, DMSO or a mixture of two or more of the these, optionally in the presence of a base such as *N*-methylmorpholine, triethylamine, diisopropylethylamine, dicyclohexylmethylamine or another tertiary amine, followed by a coupling reagent such as dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1,1'-carbonyldiimidazole, 2-(1H-9-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate or bromo-tris-pyrrolidinophosphonium hexafluorophosphate in a solvent such as DMF, NMP, THF, dichloromethane, 1,2-dichloroethane, acetonitrile, DMSO or a mixture of two or more of these, optionally in the presence of a side reaction inhibitor such as 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine, *N*-hydroxybenzotriazole or 1-hydroxy-7-azabenzotriazole. The reaction is performed between 20°C and 40°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed several times with the solvent used during the reaction.

Step C:

The Fmoc protecting group is removed eg using a solution of 20% piperidine in DMF. The reductive amination is generally known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 167) and is performed by stirring resin bound amine with an excess of ketone or aldehyde at low pH (by addition of an acid, such as acetic acid or formic acid) in a solvent such as THF, DMF, NMP, methanol, ethanol, DMSO, dichloromethane, 1,2-dichloroethane, trimethyl orthoformate, triethyl orthoformate, or a mixture of two or more of the above. As reducing agent sodium triacetoxy borohydride can be used. The reaction is performed between 20°C and 120°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed several times with the solvent used during the reaction optionally in combination with water.

Step D:

The reaction is generally known (Matthews, J.; Rivero, R. A. *J. Org. Chem.* 1997, 62, 6090-6092) and is usually performed by shaking resin bound amine with an excess of isocyanate or an equivalent such as a carbamate Lea'-X-D in a solvent such as DMF, NMP, THF, dichloromethane, 1,2-dichloroethane, DMSO or a mixture of two or more of the above and when using Lea'-X-D in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine or potassium carbonate. The reaction is performed between 20°C and 120°C, preferably between 20°C and 40°C. Excess reagent is filtered off and the resin is washed several times with the solvent used during the reaction.

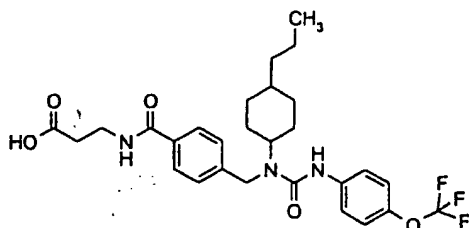
Step E:

The reaction is known (The combinatorial index, Ed. Bunin B. A., 1998, Academic press, p. 21) and is generally performed by stirring the resin bound intermediate with a 5-95% solution of TFA. The final cleavage is carried out in a solvent such as THF, dichloromethane, 1,2-dichloroethane, 1,3-dichloropropane, toluene or a mixture of two or more of the above. The reaction is performed between 0°C and 80°C, preferably between 20°C and 40°C. When the reaction is complete the product is removed by filtration. The resin is successively washed with the solvent used during the reaction, optionally containing TFA. The product and washings are collected and the solvent is removed in vacuo.

A specific example illustrating the preparation of compounds of the general formula (Ib) according to the invention is provided below.

EXAMPLE 75 (general procedure (D))

3-{4-[1-(4-Propylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-  
propionic acid

Step A: Resin bound Fmoc  $\beta$ -alanine

150  $\mu$ mol Fmoc  $\beta$ -alanine was dissolved in a mixture of 250  $\mu$ L dichloromethane, 250  $\mu$ L DMF and 100  $\mu$ L diisopropylethylamine and added to 50 mg polystyrene resin functionalized with a 2-chlorotriyl chloride linker. After shaking the suspension for 4 hours at 25°C, the resin was isolated by filtration and washed with 2 x 1 mL dichloromethane:methanol:diisopropylethylamine 17:2:1 and 2 x 1 mL DMF.

Step B: Resin bound 3-{4-[(9H-fluoren-9-ylmethoxycarbonylamino)methyl]benzoylamino}-  
propionic acid

To the above resin bound Fmoc  $\beta$ -alanine was added 500  $\mu$ L of a 20% solution of piperidine in DMF. Upon shaking 30 min, the resin was drained and washed with 1 mL DMF containing 1-hydroxybenzotriazole (50 mg/mL) and DMF (2 x 1 mL). Then 200  $\mu$ mol 4-[(9H-fluoren-9-ylmethoxycarbonylamino)methyl]benzoic acid (74.2 mg) dissolved in a mixture of 430  $\mu$ L DMF and 70  $\mu$ L diethylisopropylamine was added followed by 200  $\mu$ mol bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBrOP, 93 mg) dissolved in 500  $\mu$ L DMF. The mixture was shaken for 4 hours at 25°C followed by filtration and washing of the resin with 3 x 1 mL DMF.

Step C: Resin bound 3-{4-[(4-propylcyclohexylamino)methyl]benzoylamino}propionic acid

The Fmoc protecting group was removed from the above resin bound 3-{4-[(9H-fluoren-9-ylmethoxycarbonylamino)methyl]benzoylamino}propionic acid using 500  $\mu$ L of a 20% solution of piperidine in DMF. Upon shaking for 30 min, the resin was drained and washed with 1 mL DMF containing 1-hydroxybenzotriazole (50 mg/mL) and DMF (2 x 1 mL), 2 x 1 mL 1,2-dichloroethane and 20  $\mu$ L acetic acid dissolved in 1 mL 1,2-dichloroethane.

The resulting resin bound 3-(4-aminomethylbenzoylamino)propionic acid was treated with 98 mg 4-propylcyclohexanone (700  $\mu$ mol) dissolved in 500  $\mu$ L 1,2-dichloroethane, 50  $\mu$ L acetic acid and a slurry of 148 mg  $\text{NaBH}(\text{OAc})_3$  (700  $\mu$ mol) in 1 mL 1,2-dichloroethane. Over night shaking at 25°C followed by filtration and washing with 2 x 1 mL dichloromethane, 2 x 1 mL  $\text{CH}_3\text{OH}:\text{DMF}$  1:1 and 3 x 1 mL DMF afforded resin bound 3-{4-[(4-propylcyclohexylamino)-methyl]benzoylamino}propionic acid.

Step D: Resin bound 3-{4-[1-(4-propylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

200  $\mu$ mol 4-trifluoromethoxyphenylisocyanate dissolved in 500  $\mu$ L 1,2-dichloroethane was added to the above resin bound 3-{4-[(4-propylcyclohexylamino)methyl]benzoylamino}-propionic acid. Shaking the mixture for 5 hours at 25°C followed by filtration and washing of the resin with 2 x 1 mL dichloromethane, 4 x 1 mL DMF, 2 x 1 mL  $\text{H}_2\text{O}$ , 3 x 1 mL THF, 3 x 1 mL dichloromethane afforded the resin bound 3-{4-[1-(4-propylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid.

Step E: 3-{4-[1-(4-Propylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

The above resin bound 3-{4-[1-(4-propylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid was treated with 1 mL 5% TFA in dichloromethane for 1 hour at 25°C. The product was filtered off and the resin was washed with 1 mL dichloromethane. The combined extracts were concentrated in vacuo. The residue was dissolved in 50  $\mu$ L DMSO + 500  $\mu$ L  $\text{CH}_3\text{CN}$  and purified by preparative HPLC using a Supelcosil ABZ+ 25 cmx10 mm 5 $\mu$  column. The starting eluent composition was 5%  $\text{CH}_3\text{CN}$  in  $\text{H}_2\text{O}$  changing over 30 minutes to 90%  $\text{CH}_3\text{CN}$  in  $\text{H}_2\text{O}$  which was then kept constant for 5 minutes before going back to the starting composition over 10 min. The flow rate was kept constant at 8 mL/min. collecting one fraction per minute. The process was monitored using an UV detector operating at 214 nm. The fractions containing the desired products were combined and evaporated in vacuo to afford the title compound.

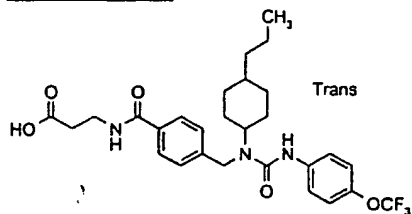
HPLC-MS (method B) ( $m/z$  = 550), (7.46, 7.58 min)

The HPLC purification allowed the separation of the *cis* and *trans* isomers of the title compound. The products were characterized by HPLC-MS and  $^1\text{H}$  NMR.



**EXAMPLE 76 (general procedure (D))**

3-{4-[1-(4-*trans*-Propylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



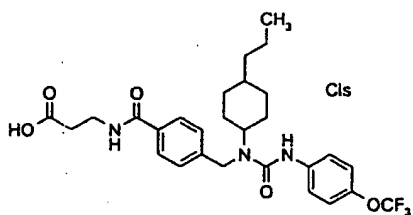
5

<sup>1</sup>H NMR (400 MHz), (DMSO-*d*<sub>6</sub>): δ 12.20 (s br, 1H); 8.55 (s, 1H); 8.50 (t, 1H); 7.75 (d, 2H); 7.55 (d, 2H); 7.30 (d, 2H); 7.20 (d, 2H); 4.60 (s, 2H); 4.10 (t, 1H); 3.40 (m, 2H); 2.45 (t, 2H); 0.70-1.80 ppm (m, 16H).

10 HPLC-MS (method B) (m/z = 550), (R<sub>t</sub> = 7.46 min).

**EXAMPLE 77 (general procedure (D))**

3-{4-[1-(4-*cis*-Propylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



15

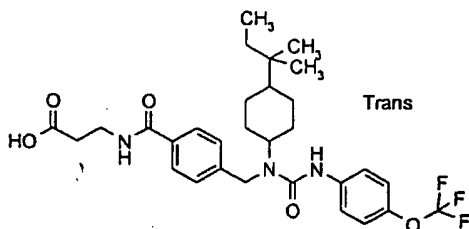
<sup>1</sup>H NMR (400 MHz), (DMSO-*d*<sub>6</sub>): δ 12.15 (s br, 1H); 8.55 (s, 1H); 8.50 (t, 1H); 7.80 (d, 2H); 7.55 (d, 2H); 7.35 (d, 2H); 7.25 (d, 2H); 4.65 (s, 2H); 4.10 (s br, 1H); 3.45 (m, 2H); 2.50 (2H); 1.15-1.65 ppm (m, 13H), 0.85 (t, 3H).

20

HPLC-MS (method B) (m/z = 550), (7.58 min).

**EXAMPLE 78 (general procedure (D))**

3-{4-[1-[4-*trans*-(1,1-Dimethylpropyl)cyclohexyl]-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



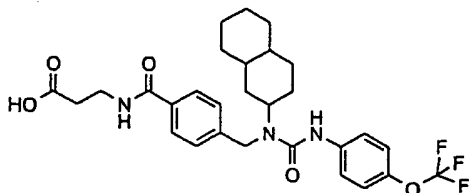
5

HPLC-MS (method B) ( $m/z$  = 578) (7.84 min, 7.94 min).

**EXAMPLE 79 (general procedure (D))**

3-{4-[1-(Decahydronaphthalen-2-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

10

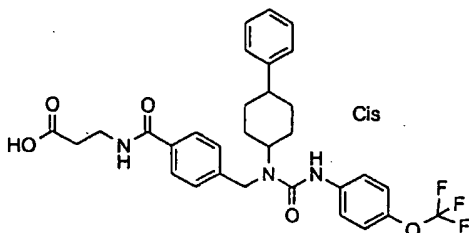


<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  8.50 (s, 1H); 8.47 (t, 1H); 7.76 (d, 2H); 7.55 (d, 2H); 7.30 (d, 2H); 7.22 (d, 2H); 4.60 (s, 2H); 4.30 (t, 1H), 3.45 (m, 2H); 2.50 (t, 2H); 1.85-0.70 (m).

15 HPLC-MS (method B) ( $m/z$  = 562) (7.48 min, 7.49 min).

**EXAMPLE 80 (general procedure (D))**

3-{4-[1-(4-*cis*-Phenylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

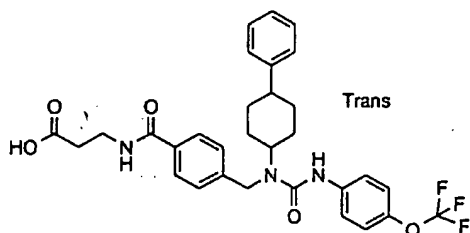


20

HPLC-MS (method B) ( $m/z$  = 584), (7.22 min, 7.33 min).

EXAMPLE 81 (general procedure (D))

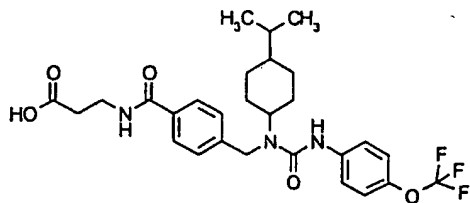
3-{4-[1-(4-*trans*-Phenylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



HPLC-MS (method B) ( $m/z$  = 584), (7.22 min, 7.33 min).

EXAMPLE 82 (general procedure (D))

10 3-{4-[1-(4-Isopropylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

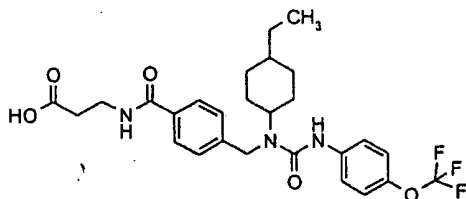


15  $^1\text{H}$  NMR (200 MHz), ( $\text{DMSO}-d_6$ ):  $\delta$  8.55 (s, 1H); 8.45 (t, 1H); 7.75 (d, 2H); 7.55 (d, 2H); 7.35 (d, 2H); 7.20 (d, 2H); 4.60 (s, 2H); 4.05-4.15 (m br, 1H); 3.45 (m, 2H); 2.50 (t, 2H); 0.90-1.8 (m, 10H); 0.85 (d, 6H).

HPLC-MS (method B) ( $m/z$  = 550), ( $R_t$  = 7.38 min, 7.50 min)

**EXAMPLE 83 (general procedure (D))**

3-[4-[1-(4-Ethylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino]propionic acid



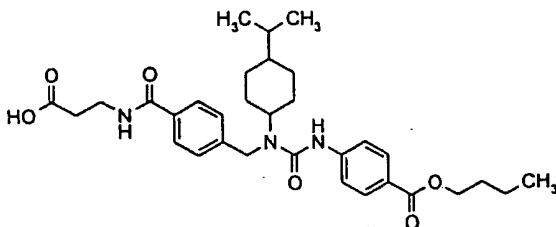
5

$^1\text{H}$  NMR (300 MHz), (DMSO- $d_6$ ):  $\delta$  8.55 (s, 1H); 8.45 (t, 1H); 7.75 (d, 2H); 7.55 (d, 2H); 7.30 (d, 2H); 7.25 (d, 2H); 4.60 (s, 2H); 4.05-4.15 (m br, 1H); 3.45 (m, 2H); 2.50 (t, 2H); 0.75-1.8 (m, 14H).

10 HPLC-MS (method B) ( $m/z$  = 536), ( $R_t$  = 7.59 min).

**EXAMPLE 84 (general procedure (D))**

4-[3-[4-(2-Carboxyethylcarbamoyl)benzyl]-3-(4-isopropylcyclohexyl)ureido]benzoic acid butyl ester

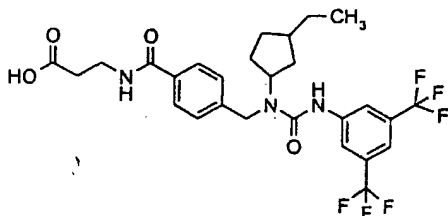


15

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  8.70 (s, 1H); 8.45 (t, 1H); 7.83 (d, 2H); 7.78 (d, 2H); 7.60 (d, 2H); 7.34 (d, 2H); 4.67 (s, 2H); 4.24 (t, 2H); 4.14 (m, 1H); 0.96 (t, 3H); 0.85 (d, 6H).

EXAMPLE 85 (general procedure (D))

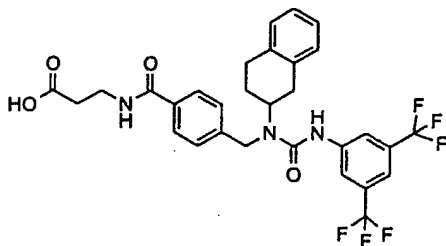
3-{4-[3-(3,5-Bis(trifluoromethyl)phenyl)-1-(3-ethylcyclopentyl)ureidomethyl]benzoylamino}-propionic acid



- 5  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  9.04 (s, 1H); 8.48 (t, 1H); 8.28 (s, 2H); 7.71 (d, 2H); 7.62 (s, 1H); 7.84 (d, 2H); 4.65 (s, 2H).

EXAMPLE 86 (general procedure (D))

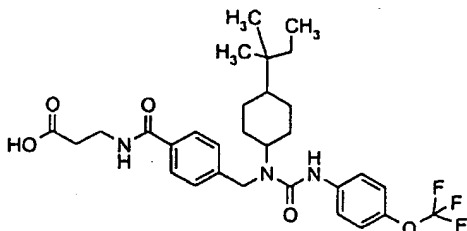
10 3-{4-[3-(3,5-Bis(trifluoromethyl)phenyl)-1-(1,2,3,4-tetrahydronaphthalen-2-yl)ureidomethyl]benzoylamino}propionic acid



- 15  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  9.20 (s, 1H); 8.50 (t, 1H); 8.82 (s, 2H); 7.81 (d, 2H); 7.62 (s, 1H); 7.42 (d, 2H); 7.10 (m, 4H); 4.75 (dd, 2H); 4.52 (m, 1H).

EXAMPLE 87 (general procedure (D))

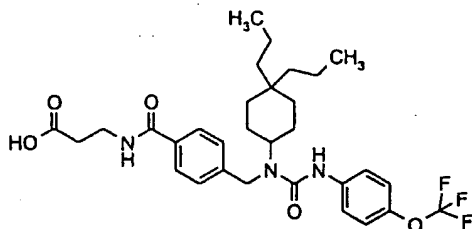
20 3-{4-[1-[4-(1,1-Dimethylpropyl)cyclohexyl]-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 12.05 (s br) 8.60 (s); 8.55 (s); 8.45 (t); 7.80 (d); 7.55 (d); 7.30 (d); 7.20 (d); 4.72 (s); 4.60 (s); 4.25 (t); 4.05 (t); 3.45 (q); 2.50 (t); 1.90-1.00 (m) 0.77 (s); 0.73 (s).

5 EXAMPLE 88 (general procedure (D))

3-{4-[1-(4,4-Dipropylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



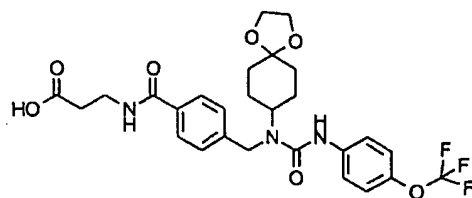
10 <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.55 (s, 1H); 8.45 (t, 1H); 7.75 (d, 2H); 7.52 (d, 2H); 7.30 (d, 2H); 7.20 (d, 2H); 4.62 (s, 2H); 4.05 (t, 1H); 3.45 (q, 2H); 2.45 (t, 2H); 1.70-0.70 (m, 22H).

HPLC-MS (method B): *m/z* = 592, *R*<sub>t</sub> = 8.60 min.

15 The compounds of the invention can also be prepared by conventional solution phase synthesis methods as described below:

EXAMPLE 89

3-{4-[1-(1,4-Dioxaspiro[4.5]dec-8-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



25 Ethyl 3-(4-aminomethylbenzoylamino)propanoate hydrochloride was prepared from β-alanine ethyl ester hydrochloride and 4-(*tert*-butoxycarbonylaminoethyl)benzoic acid by methods known to those skilled in the art.

3-{4-[(1,4-Dioxaspiro[4.5]dec-8-ylamino)methyl]benzoylamino}propionic acid ethyl ester

1.2 g Ethyl 3-(4-aminomethylbenzoylamino)propanoate hydrochloride (4.18 mmol) was mixed with 20 mL 1,2-dichloroethane and 6 mL saturated  $K_2CO_3$  by vigorous stirring. The phases were separated and the aqueous phase was extracted with another 20 mL 1,2-dichloroethane. 240  $\mu$ L HOAc was added to the combined 1,2-dichloroethane phase followed by 0.691 g 1,4-dioxaspiro[4.5]decan-8-one (4.42 mmol). 1.272 g  $NaBH(OAc)_3$  (6 mmol) was added, and the reaction was stirred for 16 hours at 25°C. The reaction volume was reduced on a rotary evaporator to about 20 mL and then poured into a mixture of 60 mL  $H_2O$  and 10 mL sat.  $K_2CO_3$ . The phases were separated and the aqueous phase was extracted twice with 40 mL 1,2-dichloroethane. The combined 1,2-dichloroethane fractions were dried over  $MgSO_4$  and evaporated to afford the title compound. The crude product was used in the next step without further purification.

3-{4-[1-(1,4-Dioxaspiro[4.5]dec-8-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid ethyl ester

0.312 g 4-Trifluoromethoxyphenylisocyanate dissolved in 1 mL acetonitrile was added to 0.5 g of the above 3-{4-[(1,4-dioxaspiro[4.5]dec-8-ylamino)methyl]benzoylamino}propionic acid ethyl ester dissolved in 5 mL acetonitrile and was allowed to react at 25°C. The product precipitated after 1 hour and was collected by filtration.

$^1H$  NMR (400 MHz), (DMSO- $d_6$ ):  $\delta$  8.55 (s, 1H); 8.50 (t, 1H); 7.75 (d, 2H); 7.50 (d, 2H); 7.30 (d, 2H); 7.20 (d, 2H); 4.60 (s, 2H); 4.20 (s br, 1H); 4.05 (q, 2H); 3.75 (s, 4H); 3.30 (m, 2H); 2.60 (t, 2H); 1.60-1.70 (m, 8H); 1.15 (t, 3H)

3-{4-[1-(1,4-Dioxaspiro[4.5]dec-8-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

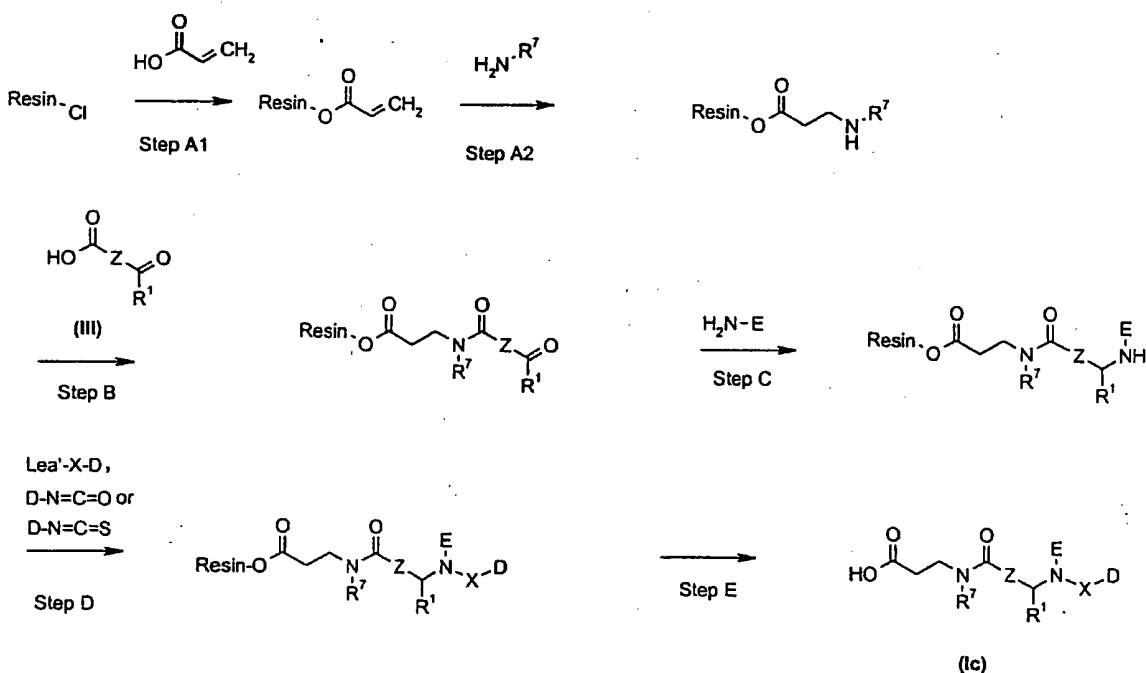
180 mg LiOH dissolved in 2.2 mL  $H_2O$  was added to the entire yield of the above 3-{4-[1-(1,4-dioxaspiro[4.5]dec-8-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid ethyl ester dissolved in 22 mL abs. EtOH. After 1 hour at 25°C the solvent was evaporated and 10 mL  $H_2O$  followed by 500 mg citric acid dissolved in 20 mL  $H_2O$  was added to the residue affording a pH of 4-5. The resulting product was a mixture of the acid and its lithium salt.

$^1\text{H}$  NMR (400 MHz), (DMSO- $d_6$ +TFA):  $\delta$  8.60 (s, 1H); 8.50 (t, 1H); 7.80 (d, 2H); 7.55 (d, 2H); 7.30 (d, 2H); 7.20 (d, 2H); 4.60 (s, 2H); 4.20 (s br, 1H); 3.80 (s, 4H); 3.45 (m, 2H); 2.50 (t, 2H); 1.55-1.75 (m, 8H).

- 5 HPLC-MS (method B) ( $m/z$  = 566 M+1), ( $R_t$  = 6.10 min).

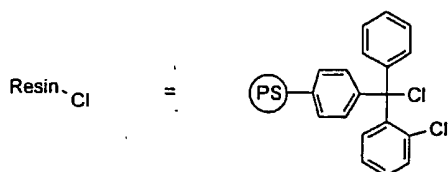
General procedure (E) for the solid phase synthesis of compounds of the general formula (Ic):

- 10 Compounds of the general formula (Ic) according to the invention can be synthesized on solid support using a procedure comprising attachment of acrylic acid to a polystyrene 2-chlorotritylchloride resin followed by a Michael addition of  $R^7\text{-NH}_2$ . Acylation followed by reductive amination and urea formation as described above affords the desired compounds:



15

wherein



wherein PS is polystyrene



Lea' is a leaving group such as -OSu, chloro, phenoxy or 4-nitrophenoxy,

R<sup>1</sup>, E and D are as defined for formula (I),

5

R<sup>7</sup> is C<sub>1-6</sub>-alkyl or C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkyl, and

X is -S(O)<sub>2</sub>-(CH<sub>2</sub>)<sub>r</sub>-, -C(O)NH- or -C(S)NH-, wherein r is as defined for formula (I),

10 Step A1:

The reaction is known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 24) and is generally performed by shaking a suspension of the resin with a solution of acrylic acid in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine. Typical solvents are pyridine, dichloromethane, 1,2-dichloroethane, DMF, NMP, THF, DMSO or mixtures of two or more of these. The reaction is performed between 20°C and 120°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed with any solvent mentioned above including mixtures hereof, containing a base as mentioned above and an alcohol, typically methanol, as a scavenger of unreacted resin bound 2-chlorotriylchloride.

20

Step A2:

The reaction is known (Hamper, B. C.; Kolodziej, S. A.; Scates, A. M.; Smith, R. G.; Cortez, E. J. *Org. Chem.* **1998**, 63, 703-718) and is performed by shaking the resin bound acrylic acid with an excess of a primary amine in a solvent such as DMSO, DMF, NMP, THF, methanol, ethanol, dichloromethane, 1,2-dichloroethane or a mixture of two or more of these. The reaction is carried out between 20°C and 120°C, preferably at 25°C. Excess amine is filtered off and the resin is washed several times with the solvent used during the reaction.

25

Step B:

The reaction is known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 78) and is performed by adding an excess of acid (III) in a solvent such as DMF, NMP, THF, dichloromethane, 1,2-dichloroethane, acetonitrile, DMSO or a mixture of the above, optionally in the presence of a base such as *N*-methylmorpholine, triethylamine, diisopropylethylamine, dicyclohexylmethylamine or another tertiary amine, followed by a coupling reagent such as dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1,1'-carbonyldiimidazole, 2-(1H-

30

35

9-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate or bromo-tris-pyrrolidinophosphonium hexafluorophosphate in a solvent such as DMF, NMP, THF, dichloromethane, 1,2-dichloroethane, acetonitrile, DMSO or a mixture of two or more of these optionally in the presence of a side reaction inhibitor such as 3-hydroxy-4-oxo-3,4-dihydro-  
5 1,2,3-benzotriazine, *N*-hydroxybenzotriazole or 1-hydroxy-7-azabenzotriazol. The reaction is performed between 20°C and 40°C, preferably at 25°C. Excess of reagents is filtered off and the resin is washed several times with the solvent used in the reaction.

Step C:

10 The reaction is generally known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 133) and is generally performed by stirring the resin bound aldehyde or ketone obtained in step B with an excess of amine at low pH (by addition of an acid, such as acetic acid or formic acid) in a solvent such as THF, DMF, NMP, methanol, ethanol, DMSO, dichloromethane, 1,2-dichloroethane, trimethyl orthoformate, triethyl orthoformate, or a mixture  
15 of two or more of these. A reducing agent such as sodium cyanoborohydride can be used. The reaction is performed between 20°C and 120°C, preferably at 25°C. Excess of reagents is filtered off and the resin is washed several times with the solvent used in the reaction optionally in combination with water.

20 Step D:

The reaction is generally known (Matthews, J.; Rivero, R. A. *J. Org. Chem.* 1997, 62, 6090-6092) and is usually performed by shaking resin bound amine obtained in step C with an excess of an isocyanate or isothiocyanate or alternatively Lea'-X-D in a solvent such as DMF, NMP, THF, dichloromethane, 1,2-dichloroethane, DMSO or a mixture of two or more of the  
25 above and when using Lea'-X-D in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine or potassium carbonate. The reaction is performed between 20°C and 120°C, preferably between 20°C and 40°C. Excess of reagent is filtered off and the resin is washed several times with the solvent used in the reaction.

30

Step E:

The reaction is known (The combinatorial index, Ed. Bunin B. A., 1998, Academic press, p. 21) and is generally performed by stirring the resin bound intermediate obtained in step D with a 5-95% solution of TFA. The final cleavage is carried out in a solvent such as THF, dichloromethane, 1,2-dichloroethane, 1,3-dichloropropane, toluene or a mixture of two or  
35

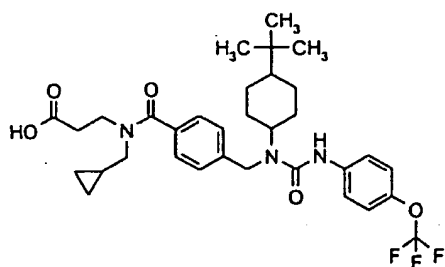
more of these. The reaction is performed between 0°C and 80°C, preferably between 20°C and 40°C. When the reaction is complete the product is removed by filtration. The resin is successively washed with the solvent used in the reaction, optionally containing TFA. The product and washings are collected. The solvent is removed in vacuo.

5

The following examples were prepared according to general procedure (E).

EXAMPLE 90 (general procedure (E))

3-({4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl}-  
10 cyclopropylmethyl)aminopropionic acid



Step A1: Resin bound acrylic acid

15 150  $\mu$ mol acrylic acid was dissolved in a mixture of 500  $\mu$ L dichloromethane and 100  $\mu$ L diisopropylethylamine and added to 50 mg polystyrene resin functionalized with a 2-chlorotriyl chloride linker. After shaking the suspension for 4 hours at 25°C, the resin was isolated by filtration and washed with 2 x 1 mL dichloromethane: methanol: diisopropylethylamine 17:2:1 and 2 x 1 mL DMSO.

20 Step A2: Resin bound *N*-(cyclopropylmethyl)-3-aminopropionic acid

The above resin bound acrylic acid (50 mg) was treated with 300  $\mu$ mol cyclopropylmethyl amine (21.3 mg) in 300  $\mu$ L DMSO for 72 hours at 25°C. The excess reagent was filtered off and the resin was washed with 3 x 1 mL DMSO and 3 x 1 mL DMF.

25 Step B: Resin bound 3-[cyclopropylmethyl-(4-formylbenzoyl)amino]propionic acid

To the above resin bound *N*-(cyclopropylmethyl) 3-aminopropionic acid (50 mg) was added 200  $\mu$ mol 4-formylbenzoic acid (30 mg) dissolved in a mixture of 430  $\mu$ L DMF and 70  $\mu$ L diisopropylethylamine followed by 200  $\mu$ mol bromo-tris-pyrrolidinophosphonium hexafluorophosphate (PyBrOP, 93 mg) dissolved in 500  $\mu$ L DMF. The mixture was shaken at 25°C for 4

hours followed by filtration and washing of the resin with 3 x 1 mL DMF and 1 mL trimethylorthoformate.

Step C: Resin bound 3-({4-[1-(4-*tert*-butylcyclohexylamino)methyl]benzoyl}cyclopropylmethyl-  
amino)propionic acid

The above resin bound 3-[cyclopropylmethyl-(4-formylbenzoyl)amino]propionic acid (50 mg) was treated with 1 mL 0.5 M (0.5 mmol, 77.5 mg) 4-*tert*-butylcyclohexylamine solution in DMF:trimethylorthoformate 1:1, 100  $\mu$ L glacial acetic acid and sodium cyanoborohydride (750  $\mu$ mol, 48 mg) suspended in 0.5 mL DMF:trimethylorthoformate 1:1. Overnight shaking at 25°C followed by filtration and washing with 2 x 1 mL 20% H<sub>2</sub>O in DMF, 3 x 1 mL DMF and 2 x 1 mL dichloromethane afforded the desired product.

Step D: Resin bound 3-({4-[1-(4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)-ureidomethyl]benzoyl}cyclopropylmethyl)aminopropionic acid

200  $\mu$ mol 4-trifluoromethoxyphenylisocyanate dissolved in 500  $\mu$ L dichloromethane was added to the above resin bound 3-({4-[1-(4-*tert*-butylcyclohexylamino)methyl]benzoyl}-cyclopropylmethyl)aminopropionic acid (50 mg). Shaking the mixture 5 hours at 25°C followed by filtration and washing of the resin with 2 x 1 mL dichloromethane, 4 x 1 mL DMF, 2 x 1 mL H<sub>2</sub>O, 3 x 1 mL THF and 3 x 1 mL dichloromethane afforded the resin bound title compound.

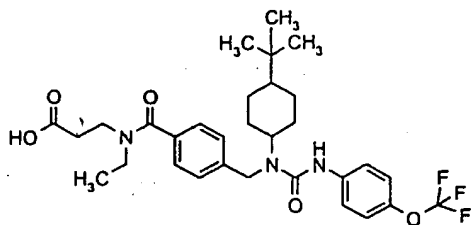
Step E: 3-({4-[1-(4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl}-cyclopropylmethyl)aminopropionic acid

The above resin bound 3-({4-[1-(4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)-ureidomethyl]benzoyl}cyclopropylmethyl)aminopropionic acid (50 mg) was treated with 1 mL 5% TFA in dichloromethane for 1 hour at 25°C. The product was filtered off and the resin was washed with 1 mL dichloromethane. The combined extracts were concentrated in vacuo. The residue was dissolved in 50  $\mu$ L DMSO + 500  $\mu$ L acetonitrile and purified by preparative HPLC using a Supelcosil ABZ+ 25 cm x 10 mm 5 $\mu$  column. The starting eluent composition was 5% acetonitrile in water changing over 30 min to 90% acetonitrile in water which was then kept constant for 5 min before going back to the starting composition over 10 min. The flow rate was kept constant at 8 mL/min collecting one fraction per minute. The process was monitored using an UV detector operating at 214 nm. The fractions containing the desired product were combined and evaporated in vacuo to afford the title compound.

The product was characterized by HPLC-MS (Method B): R<sub>t</sub> = 7.91 min, m/z = 618 (M+1).

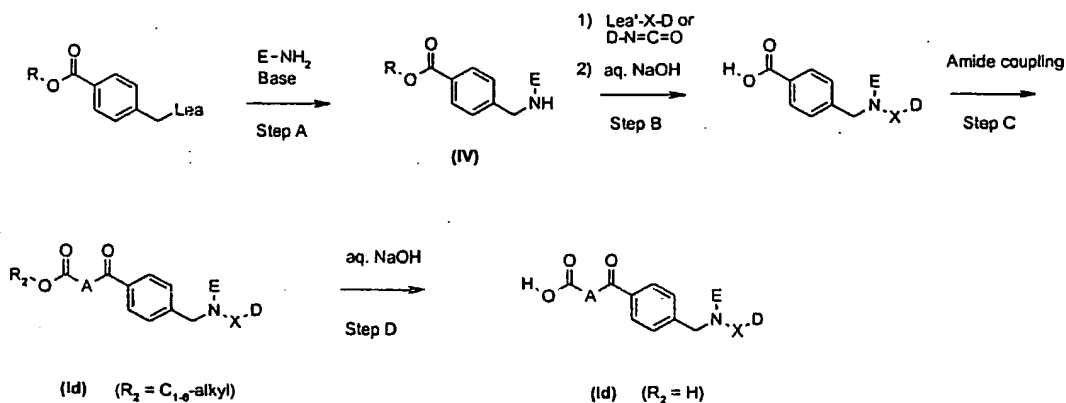
EXAMPLE 91 (general procedure (E))

3-({4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl}ethyl-amino)propionic acid



The product was characterized by HPLC-MS (Method B):  $R_t = 7.94$  min,  $m/z = 592$  (M+1).

The compounds of the invention can also be prepared by conventional solution phase synthesis methods as the following general method describes.

General procedure (F) for the solution phase synthesis of compounds of general formula (Id):

wherein R is  $C_{1-6}$ -alkyl,

A, X, D, and E are as defined in general formula (I),

Lea is a leaving group such as chloro, bromo, iodo, mesyl, or tosyl, and

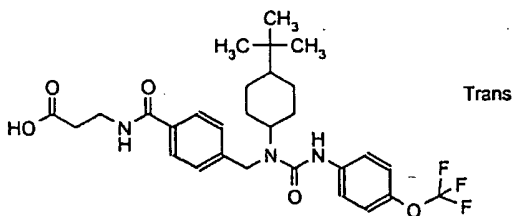
Lea' is a leaving group such as -OSu, chloro, phenoxy, or 4-nitrophenoxy.

In case the intermediate of the formula (IV) is a mixture of isomers, separation of these may be performed eg by column chromatography of the intermediate of the formula (IV) or crystallisation of the intermediate imine.

- 5 The procedure is illustrated in example 92.

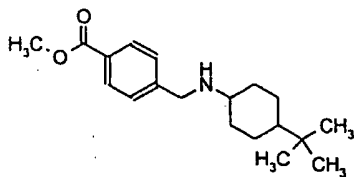
EXAMPLE 92 (general procedure (F))

3-{4-[1-(4-*trans*-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl-amino}propionic acid



10

Step A: 4-[(4-*tert*-Butylcyclohexylamino)methyl]benzoic acid methyl ester



- 15 4-(Bromomethyl)benzoic acid methyl ester (5.0 g, 22 mmol) and 4-*tert*-butylcyclohexylamine (*cis/trans* mixture) (3.4 g, 22 mmol) were dissolved in DMF where after potassium carbonate (6.1 g, 44 mmol) was added. The reaction mixture was stirred at 100°C for 7 hours and for 16 hours at 20°C. Water (100 mL) and ethyl acetate (200 mL) were added to the reaction mixture. The organic phase was isolated and washed with water (2 x 100 mL) and a saturated solution of sodium chloride (2 x 100 mL). The organic phase was dried (MgSO<sub>4</sub>), filtered and concentrated in vacuo to give a *cis/trans* mixture of 4-[(4-*tert*-butylcyclohexylamino)methyl]-benzoic acid methyl ester as a crude product. The two isomers were separated on silica (110 g) using a mixture of ethyl acetate and dichloromethane (7:3) as eluent.
- 20

*trans* isomer:

Micro analysis: Calculated for  $C_{19}H_{29}NO_2$ :

C: 75.21, H: 9.63, N: 4.62%. Found:

C: 75.02, H: 9.80, N: 4.64%.

5

HPLC-MS (Method B):  $R_t = 5.23$  min,  $m/z = 304$  ( $M + 1$ ).

$^1H$  NMR ( $DMSO-d_6$ ), 400 MHz:  $\delta$  7.90 (d, 2H), 7.48 (d, 2H), 3.82 (s, 3H), 3.78 (s, 2H), 2.30-2.20 (m, 1H), 2.05-1.90 (m, 3H), 1.73-1.65 (m, 2H), 1.10-0.90 (m, 4H), 0.80 (s, 9H).

10

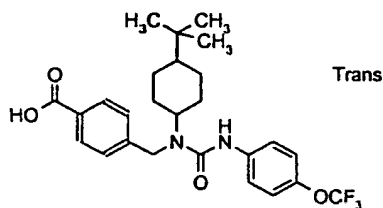
*cis* isomer:

HPLC-MS (Method B):  $R_t = 4.83$  min,  $m/z = 304$  ( $M + 1$ ).

$^1H$  NMR ( $DMSO-d_6$ ), 400 MHz:  $\delta$  7.92 (d, 2H), 7.58 (d, 2H), 3.90 (dd, 1H), 3.85 (s, 3H), 3.80 (dd, 1H), 2.50-2.35 (m, 1H), 2.00-1.85 (m, 2H), 1.80-1.70 (m, 2H), 1.70-1.45 (m, 2H), 1.00-0.80 (m, 1H), 0.80 (s, 9H).

15

Step B: 4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid



20

4-[(*trans*-4-*tert*-Butylcyclohexylamino)methyl]benzoic acid methyl ester (2.6 g, 8.6 mmol) and 4-(trifluoromethoxy)phenyl isocyanate (1.7 g, 8.6 mmol) were dissolved in acetonitrile (40 mL) and stirred at 20°C for 16 hours. The reaction mixture was concentrated in vacuo and the crude product purified on silica (100 g) using heptane and ethyl acetate (3:1) as eluent to give 4-[1-(*trans*-4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid methyl ester. The product was suspended in ethanol (80 mL) and sodium hydroxide (4N, 17 mL) was added. The reaction mixture was stirred at 50°C for 3 hours and then concentrated in vacuo until all ethanol was removed. The reaction mixture was diluted with water (100 mL) and adjusted to pH 2 with hydrochloric acid (4N). The aqueous phase was extracted with ethyl acetate (3 x 75 mL) and the combined organic phases were dried ( $MgSO_4$ ) and concen-

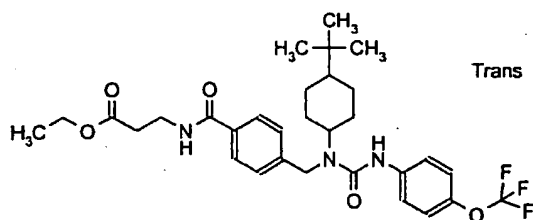
30

trated in vacuo to give 4-[1-(*trans*-4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)-ureidomethyl]benzoic acid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>), 400 MHz: δ 12.80 (s, 1H), 8.55 (s, 1H), 7.90 (d, 2H), 7.55 (d, 2H), 7.35 (d, 2H), 7.21 (d, 2H), 4.62 (s, 2H), 4.10-4.00 (m, 1H), 2.00 (s, 2H), 1.80-1.60 (m, 4H), 1.48-1.38 (m, 2H), 1.20-1.00 (m, 2H), 1.00-0.88 (m, 1H), 0.80 (s, 9H).

HPLC-MS (Method B): R<sub>t</sub> = 8.37 min, m/z = 493 (M + 1).

10 Step C: 3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino}propionic acid ethyl ester



4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid (2.0 g, 4.1 mmol), 1-hydroxybenzotriazole (0.6 g, 4.3 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.8 g, 4.3 mmol) were dissolved in DMF (40 mL). A solution of diisopropylethylamine (0.5 g, 4.1 mmol) and 3-aminopropionic acid ethyl ester, hydrochloride (0.4 g, 4.3 mmol) in DMF (10 mL) was added and the reaction mixture was stirred for 16 hours at 20°C. Ethyl acetate (150 mL) and water (100 mL) were added and the organic phase isolated. The aqueous phase was extracted with ethyl acetate (50 mL) and the organic phases combined, dried (MgSO<sub>4</sub>) and concentrated in vacuo. The crude product was purified on silica (80 g) using heptane and ethyl acetate (1:1) as eluent to give 3-{4-[1-(*trans*-4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid ethyl ester.

25

M.p. = 108-111°C.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>), 400 MHz: δ 8.55 (s, 1H), 8.50 (t, 1H), 7.75 (d, 2H), 7.55 (d, 2H), 7.31 (d, 2H), 7.22 (d, 2H), 4.60 (s, 2H), 4.10-4.00 (m, 1H), 3.60 (s, 3H), 3.45 (dd, 2H), 2.55 (t, 2H), 1.80-1.60 (m, 4H), 1.50-0.80 (m, 5H), 0.80 (s, 9H).

30



HPLC-MS (Method B):  $R_t = 8.43$  min,  $m/z = 578$  ( $M + 1$ ).

Step D:

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl-  
5 amino}propionic acid ethyl ester (1.4 g, 2.4 mmol) was suspended in ethanol (50 mL) and  
sodium hydroxide (4 N, 6 mL) added. The reaction mixture was stirred for 2 hours at 50°C  
and then concentrated in vacuo until all ethanol was removed. The reaction mixture was di-  
luted with water (100 mL) and adjusted to pH 2 with hydrochloric acid (4N), and the title  
compound was isolated by filtration.

10

M.p. = 152-154°C.

$^1\text{H}$  NMR (DMSO- $d_6$ ), 400 MHz:  $\delta$  12.20 (s, 1H), 8.55 (s, 1H), 7.95 (t, 1H), 7.75 (d, 2H), 7.55  
(d, 2H), 7.31 (d, 2H), 7.22 (d, 2H), 4.60 (s, 2H), 4.10-4.00 (m, 1H), 3.45 (dd, 2H), 2.50 (2H),  
15 1.80-1.60 (m, 4H), 1.45-1.35 (m, 2H), 1.15-1.05 (m, 2H), 0.95-0.85 (m, 1H), 0.80 (s, 9H).

HPLC-MS (Method B):  $R_t = 7.88$  min,  $m/z = 564$  ( $M + 1$ ).

Micro analysis: Calculated for  $\text{C}_{29}\text{H}_{36}\text{F}_3\text{N}_3\text{O}_5$ ,  $0.75\text{H}_2\text{O}$ :

20 C: 60.35, H: 6.55, N: 7.28%. Found:

C: 60.47, H: 6.32, N: 7.32%.

Alternative method for the preparation of the compound (general procedure (K)):

General procedure (K) is described in the following:

Step 6, using pure isocyanate prepared from (substituted) anilines and diphosgene as described under the general procedure (K):

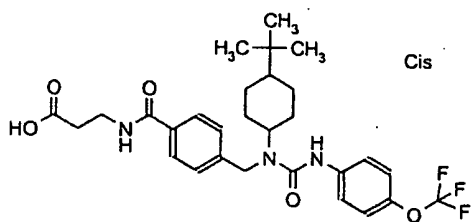
- 5 Methyl *trans*-4-[(4-*tert*-butylcyclohexyl)aminomethyl]benzoylaminopropanoate, hydrochloride (10.0 g 24 mmol, prepared by using anhydrous hydrogen chloride in ethyl acetate in general procedure (K), step 5) was suspended in acetonitrile (300 mL) and diisopropylethylamine (4.14 mL, 24 mmol) was added. To this suspension 4-trifluoromethoxyphenylisocyanate
- 10 (3.75 mL, 24 mmol) was added. Stirring at room temperature was continued for 4 hours and then the mixture was left at 5°C for 16 hours. Filtration and washing with cold acetonitrile afforded 11.9 g (85%) of 3-{4-[1-(4-*trans*-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)-ureidomethyl]benzoylamino}propionic acid methyl ester.

15 Step 7:

Hydrolysis of this ester using the method described in example 46, step D afforded the title compound (11 g, 94%).

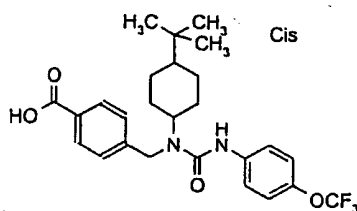
EXAMPLE 93

- 20 3-{4-[1-(*cis*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxy-phenyl)ureidomethyl]-benzoylamino}propionic acid



Step A: 4-[1-(*cis*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid

- 25



4-[(*cis*-4-*tert*-Butylcyclohexylamino)methyl]benzoic acid methyl ester (0.36 g, 1.2 mmol) and 4-(trifluoromethoxy)phenyl isocyanate (0.24 g, 1.2 mmol) were dissolved in acetonitrile (10 mL) and stirred at 20°C for 16 hours. The reaction mixture was concentrated in vacuo and the crude product purified on silica (25 g) using heptane and ethyl acetate (9:1) as eluent to give 4-[1-(*cis*-4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid methyl ester. The product was suspended in ethanol (10 mL) and sodium hydroxide (4N, 1.1 mL) was added. The reaction mixture was stirred at 50°C for 3 hours and then concentrated in vacuo until all ethanol was removed. The reaction mixture was diluted with water (50 mL) and adjusted to pH 2 with hydrochloric acid (4N). The aqueous phase was extracted with ethyl acetate (75 mL) and the organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo to give 4-[1-(*cis*-4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid.

Micro analysis: Calculated for C<sub>28</sub>H<sub>31</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>:

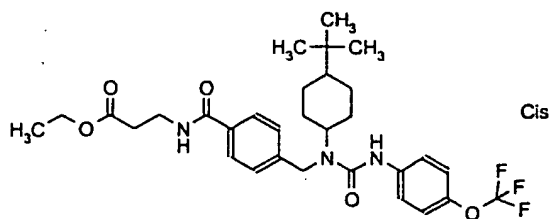
C: 63.40, H: 6.34, N: 5.69%. Found:

C: 63.29, H: 6.33, N: 5.65%.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>), 400 MHz: δ 12.80 (s, 1H), 8.61 (s, 1H), 7.90 (d, 2H), 7.55 (d, 2H), 7.35 (d, 2H), 7.22 (d, 2H), 4.72 (s, 2H), 4.32-4.22 (m, 1H), 1.85-1.70 (m, 2H), 1.65-1.45 (m, 4H), 1.40-1.10 (m, 3H), 0.80 (s, 9H).

HPLC-MS (Method B): R<sub>t</sub> = 7.85 min, m/z = 493 (M + 1).

Step B: 3-[4-[1-(*cis*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino]propionic acid ethyl ester



4-[1-(*cis*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid (0.3 g, 0.6 mmol), 1-hydroxybenzotriazole (0.1 g, 0.7 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.13 g, 0.7 mmol) were dissolved in DMF (10 mL). Diisopropylethylamine (0.1 g, 0.7 mmol) and 3-aminopropionic acid ethyl ester, hydrochloride (0.07 g, 0.7

mmol) in DMF was added and the reaction mixture was stirred for 16 hours at 20°C. Ethyl acetate (80 mL) and water (50 mL) were added and the organic phase isolated. The aqueous phase was extracted with ethyl acetate (50 mL) and the organic phases combined, dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was crystallised from heptane and ethyl acetate (4:1) to give 3-{4-[1-(*cis*-4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid ethyl ester.

M.p. = 87-90°C.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>), 400 MHz: δ 8.60 (s, 1H), 8.48 (t, 1H), 7.75 (d, 2H), 7.52 (d, 2H), 7.28 (d, 2H), 7.21 (d, 2H), 4.70 (s, 2H), 4.30-4.20 (m, 1H), 3.60 (s, 3H), 3.48 (dd, 2H), 2.55 (t, 2H), 1.82-1.70 (m, 2H), 1.60-1.45 (m, 4H), 1.40-1.10 (m, 3H), 0.80 (s, 9H).

HPLC-MS (Method B): R<sub>t</sub> = 7.80 min, m/z = 578 (M + 1).

Micro analysis: Calculated for C<sub>30</sub>H<sub>38</sub>F<sub>3</sub>N<sub>3</sub>O<sub>5</sub>:

C: 62.38, H: 6.63, N:7.27%. Found:

C: 62.49, H: 6.75, N:7.20%.

#### 20 Step C:

3-{4-[1-(*cis*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid ethyl ester (0.2 g, 0.3 mmol) was suspended in ethanol (8 mL) and sodium hydroxide (4N, 0.6 mL) added. The reaction mixture was stirred for 16 hours at 20°C and then concentrated in vacuo until all ethanol was removed. The reaction mixture was diluted with water (50 mL) and adjusted to pH 2 with hydrochloric acid (4N). The aqueous phase was extracted with ethyl acetate (80 mL) and the organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo to give the title compound.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>), 400 MHz: δ 12.20 (s, 1H), 8.60 (s, 1H), 8.45 (t, 1H), 7.77 (d, 2H), 7.53 (d, 2H), 7.28 (d, 2H), 7.20 (d, 2H), 4.70 (s, 2H), 4.30-4.20 (m, 1H), 3.45 (dd, 2H), 2.50 (2H), 1.82-1.70 (m, 2H), 1.60-1.45 (m, 4H), 1.40-1.30 (m, 2H), 1.20-1.10 (m, 1H), 0.80 (s, 9H).

HPLC-MS (Method B): R<sub>t</sub> = 7.32 min, m/z = 564 (M + 1).

35 Micro analysis: Calculated for C<sub>29</sub>H<sub>36</sub>F<sub>3</sub>N<sub>3</sub>O<sub>5</sub>, 0.25H<sub>2</sub>O:

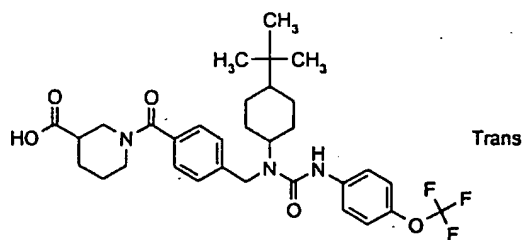
C: 61.53, H: 6.54, N: 7.18%. Found:

C: 61.36, H: 6.80, N: 7.09%.

The following compounds were prepared using the general procedure (F) as described above.

EXAMPLE 94 (general procedure (F))

1-[4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl]-piperidine-3-carboxylic acid



The compound was prepared using nipecotic acid methyl ester, hydrochloride instead of 3-aminopropionic acid methyl ester, hydrochloride in step C.

HPLC-MS (Method B):  $R_t = 8.17$  min,  $m/z = 604$  ( $M + 1$ ).

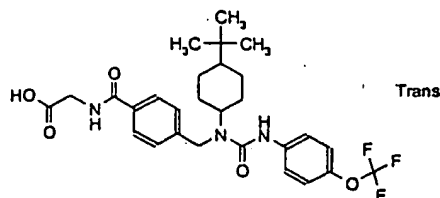
Micro analysis: Calculated for  $C_{32}H_{40}F_3N_3O_5$ :

C: 63.67, H: 6.68, N: 6.96%. Found:

C: 63.66, H: 6.75, N: 6.94%.

EXAMPLE 95 (general procedure (F))

3-[4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino]acetic acid



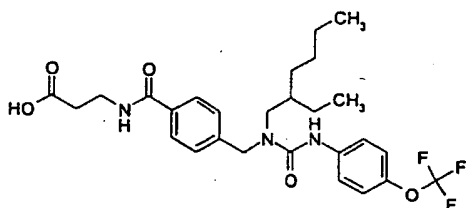
The compound was prepared using glycine methyl ester, hydrochloride instead of 3-aminopropionic acid methyl ester, hydrochloride in step C.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>), 400 MHz: δ 12.55 (s, 1H), 8.76 (t, 1H), 8.52 (s, 1H), 7.81 (d, 2H), 7.55 (d, 2H), 7.33 (d, 2H), 7.22 (d, 2H), 4.61 (s, 2H), 4.10-4.00 (m, 1H), 3.80 (d, 2H), 1.75-1.60 (m, 4H), 1.45-1.30 (m, 2H), 1.20-1.00 (m, 2H), 1.00-0.80 (m, 1H), 0.80 (s, 9H).

HPLC-MS (Method B): *R*<sub>t</sub> = 7.88 min, *m/z* = 550 (*M* + 1).

EXAMPLE 96 (general procedure (F))

3-{4-[1-(2-Ethylhexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



The compound was prepared using 2-ethylhexylamine instead of 4-*tert*-butylcyclohexylamine in step A.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>), 400 MHz: δ 12.20 (s, 1H), 8.63 (s, 1H), 8.49 (t, 1H), 7.82 (d, 2H), 7.54 (d, 2H), 7.31 (d, 2H), 7.22 (d, 2H), 4.65 (s, 2H), 3.45 (dd, 2H), 3.25 (m, 2H), 2.50 (2H), 1.70-1.60 (m, 1H), 1.40-1.10 (m, 8H), 0.90-0.70 (m, 6H).

HPLC-MS (Method B): *R*<sub>t</sub> = 7.17 and 7.25 min, *m/z* = 538 (*M* + 1).

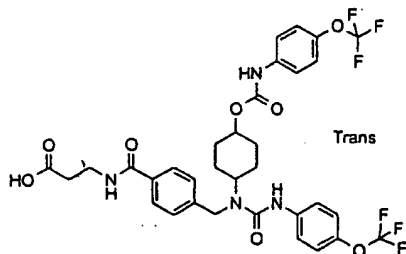
Micro analysis: Calculated for C<sub>27</sub>H<sub>34</sub>F<sub>3</sub> N<sub>3</sub>O<sub>5</sub>:

C: 60.33, H: 6.37, N: 7.82%. Found:

C: 60.51, H: 6.60, N: 7.48%.

**EXAMPLE 97**

3-[4-[1-(*trans*-4-(4-Trifluoromethoxyphenyl)carbamoyloxy)cyclohexyl]-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



5

This compound was prepared on solid support using the same methodology as described in general procedure (F) using *trans* 4-hydroxycyclohexylamine instead of 4-*tert*-butylcyclohexylamine.

10 HPLC-MS (Method B):  $R_t = 7.68$  min,  $m/z = 727$  ( $M + 1$ ).

Micro analysis: Calculated for  $C_{33}H_{32}F_3N_4O_8$ :

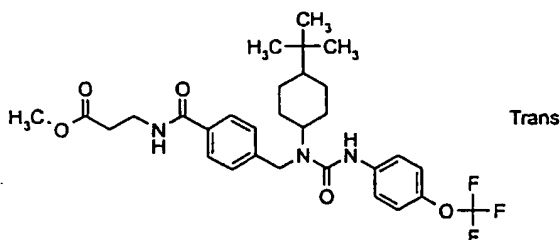
C: 54.55, H: 4.44, N: 7.71%. Found:

C: 54.17, H: 4.53, N: 7.44%.

15

**EXAMPLE 98 (general procedure (F))**

3-[4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid methyl ester



20

The compound was prepared according to procedure (F) but omitting step D.

Micro analysis: Calculated for  $C_{29}H_{36}F_3N_3O_5 \cdot 0.1H_2O$ :

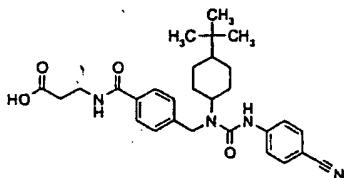
C, 61.87%; H, 6.44%; N, 7.46%. Found:

25 C, 61.60%; H, 6.45%; N, 7.43%.

HPLC-MS (Method B):  $m/z$ : 564.

EXAMPLE 99 (general procedure (F))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-cyanophenyl)ureidomethyl]benzoylamino}propionic acid

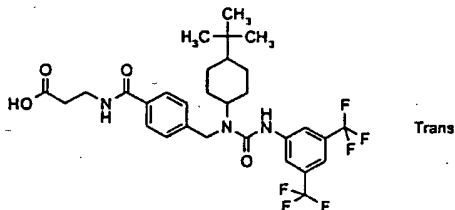


$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  12.2 (1H, broad), 8.82 (1H, s), 8.48 (1H, t), 7.78 (2H, d), 7.68 (4H, s), 7.32 (2H, d), 4.62 (2H, s), 4.05 (1H, m), 3.42 (2H, dd), 1.80-85 (9H, m), 0.80 (9H, s)

HPLC-MS (method B):  $m/z$ : 505,  $R_t$  = 7.28 min.

EXAMPLE 100 (general procedure (F))

3-{4-[3-(3,5-Bis-trifluoromethylphenyl)-1-(*trans*-4-*tert*-butylcyclohexyl)ureidomethyl]benzoyl-amino}propionic acid



The starting material, 4-[(*trans*-4-*tert*-butylcyclohexylamino)methylbenzoic acid methyl ester, was prepared as described in step A of the general procedure (F).

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  12.2 (s, 1H), 9.05(s, 1H), 8.45 (t, 1H), 8.25(s, 2H), 7.76(d, 2H), 7.61(s, 1H), 7.32(d, 2H), 4.63(s, 2H), 4.05(m, 1H), 3.45(m, 2H), 1.80-0.75 (m, 9H), 0.82 (s, 9H)

HPLC-MS (method B):  $m/z$ : 616,  $R_t$  = 8.3 min.

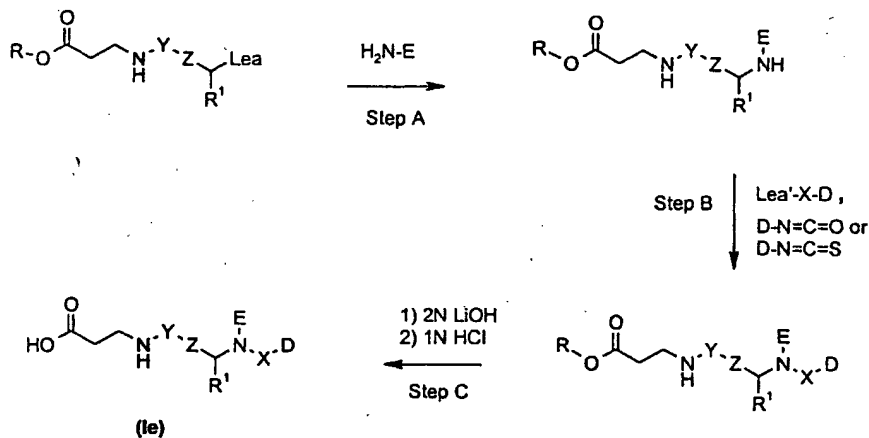
MA: calculated for  $\text{C}_{30}\text{H}_{35}\text{F}_6\text{N}_3\text{O}_4$ :

58.53% C; 5.73% H; 6.83% N; Found

58.25% C; 5.75% H; 7.02% N.



General procedure (G) for the solution phase synthesis of compounds of the general formula (le):



5

wherein

R<sup>1</sup>, E, Z and D are as defined for formula (I),

10 X is -S(O)<sub>2</sub>-(CH<sub>2</sub>)<sub>r</sub>-, -C(O)NH- or -C(S)NH-, wherein r is as defined for formula (I),

Y is -C(O)- or -S(O)<sub>2</sub>-,

R is C<sub>1-8</sub>-alkyl,

15

Lea is a leaving group such as chloro, bromo, iodo, mesyl or tosyl, and

Lea' is a leaving group such as -OSu, chloro, phenoxy, 4-nitrophenoxy.

20 Step A:

The appropriate alkylhalide (0.02 mmol) in DMF was dispensed into the wells of a deepwell plate containing solid potassium carbonate (3 equivalents) and the appropriate amine, NH<sub>2</sub>-E, (0.02 mmol). The reactions were agitated at room temperature for four hours and at 50°C for 12 hours. The solids were filtered off and the desired amines were used without further purification in the next step.

25

Step B:

To the amines in DMF was added the desired isocyanate or isothiocyanate or alternatively Lea'-X-D (0.02 mmol) in DMF. When using Lea'-X-D a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any tertiary amine or potassium carbonate was  
5 also added. The reactions are shaken for 30 minutes to give the desired ureas or thioureas.

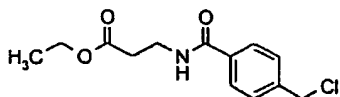
Step C:

To the crude products obtained in step B was added aqueous 2 N LiOH (10 equivalents). The samples were shaken overnight and filtered. Aqueous 1 N HCl was then added to give  
10 the desired carboxylic acids.

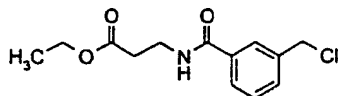
General preparation of halomethylarylcarboxamides as starting materials:

The halomethylarylcarboxamides were prepared from the coupling of the corresponding halomethylarylcarboxylic acid and the methyl or ethyl-3-aminopropionate hydrochloride accord-  
15 ing to the procedure described below.

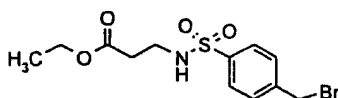
To a solution of the arylcarboxylic acid in a suitable solvent such as CH<sub>2</sub>Cl<sub>2</sub>, DMF or THF was added diisopropylethylamine (3 eq) and HBTU (1.1 eq). The reaction was allowed to stir for 30 minutes before ethyl or methyl-3-aminopropionate hydrochloride (1.1 eq) was added.  
20 The solution was stirred at room temperature for 4 hours. The solvents were evaporated under reduced pressure. The residue was taken up in ethyl acetate and 1N HCl. The organic layer was separated and washed with H<sub>2</sub>O (2 x), aqueous NaHCO<sub>3</sub> (3 x), brine (2 x), dried over MgSO<sub>4</sub> and concentrated to give the desired product.

25 Ethyl 3-[(4-(chloromethyl)benzoyl]amino}propionate:

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.2 (t, 3H), 2.6 (t, 2H), 3.5 (qt, 2H), 4.1 (qt, 2H), 4.8 (s, 2H), 7.6 (d, 2H), 7.8 (d, 2H), 8.6 (t, 1H).

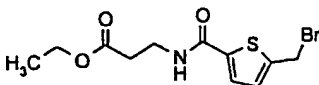
Ethyl 3-([3-(chloromethyl)benzoyl]amino)propionate:

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.61 (t, 2H), 3.50 (qt, 2H), 3.61 (s, 3H), 4.81 (s, 2H), 7.47 (t, 1H), 7.59 (d, 1H), 7.79 (d, 1H), 7.90 (s, 1H), 8.62 (brd t, 1H).

Ethyl 3-([4-(bromomethyl)phenyl]sulfonyl)amino)propionate:

To a solution of the 4-bromomethylphenylsulfonylchloride (10 g, 37 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) at 0°C was added diisopropylethylamine (16 mL, 93 mmol) followed by ethyl-3-aminopropionate hydrochloride (5.1 g, 37 mmol). The reaction was stirred for 10 minutes at 0°C and the solvent was evaporated at room temperature under reduced pressure. The residue was dissolved in ethyl acetate and washed with 1N HCl (3x), H<sub>2</sub>O, aqueous NaHCO<sub>3</sub> (3x), brine (3x) and dried over MgSO<sub>4</sub>. The solvent was concentrated to give a syrup. Addition of ethyl ether induced crystallization of the product as a white solid (10 g, 30 mmol, 81%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.24 (t, 3H), 2.55 (t, 2H), 3.22 (qt, 2H), 4.13 (qt, 2H), 4.50 (s, 2H), 5.28 (t, 1H), 7.53 (d, 2H), 7.85 (d, 2H).

Ethyl 3-([5-(bromomethyl)-2-thienyl]carbonyl)amino)propionate:

To a solution of methylthiophene carboxylic acid (20 g, 0.14 mol) in DMF (30 mL) was added at 0°C carbonyldimidazole (23 g, 0.14 mol) in portions of 10 g. After stirring at 0°C for 1 hour, a solution of ethyl 3-aminopropionate hydrochloride (21 g, 0.14 mol) in DMF (30 mL) was added followed by triethylamine (20 mL, 0.14 mol). The mixture was stirred at ambient temperature for 16 hours, filtered by suction, and the filtrate was concentrated. The residue was dissolved in ethyl acetate (100 mL), washed with water (2 x 50 mL), 1N hydrochloric

acid (2 x 50 mL), sodium bicarbonate solution (2 x 50 mL), brine (50 mL), dried (MgSO<sub>4</sub>), and concentrated. Addition of hexane to the residue induced the crystallization of ethyl 3-(((5-methyl-2-thienyl)carbonyl)amino)propionate (27 g, 80%).

- 5 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.28 (t, 3H), 2.50 (s, 3H), 2.62 (t, 2H), 3.68 (q, 2H), 4.17 (q, 2H), 6.60 (brd s, 1H), 6.66 (d, 1H), 7.30 (d, 1H).

The above product (27 g, 0.11 mol) was dissolved in carbon tetrachloride (150 mL). *N*-bromosuccinimide (21 g, 0.12 mol) and AIBN (200 mg) was added. The mixture was refluxed  
10 for 5 hours, and filtered by suction. The solid was extracted with ethyl acetate until the filtrate appeared colourless. The combined ethyl acetate extracts (200 mL) were washed with water (2 x 50 mL), dried over MgSO<sub>4</sub> and concentrated. The residue was recrystallized from hexane, ethyl acetate 1:1 to give ethyl 3-(((5-(bromomethyl)-2-thienyl)carbonyl)amino)propionate as a white solid (15 g, 41%).

- 15 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.28 (t, 3H), 2.63 (t, 2H), 3.69 (t, 2H), 4.18 (q, 2H), 4.68 (s, 2H), 7.06 (brd s, 1H), 7.07 (d, 1H), 7.32 (d, 1H).

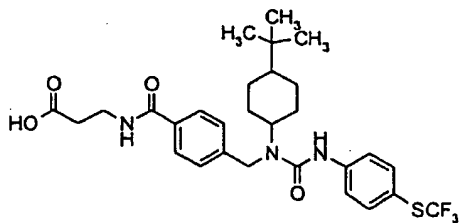
MS (APCI, neg.): 320, 318.

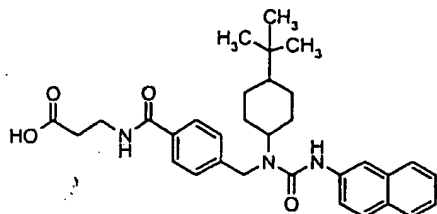
20

The following examples were prepared according to the general procedure (G).

EXAMPLE 101 (general procedure (G))

- 25 3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]benzoyl-amino}propionic acid

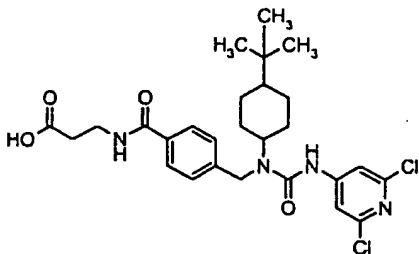


EXAMPLE 102 (general procedure (G))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-naphthalen-2-ylureidomethyl]benzoylamino}propionic acid

5

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.83 (s, 9H), 0.91 (m, 1H), 1.11 (m, 2H), 1.40 (m, 2H), 1.67-1.76 (m, 4H), 2.44 (t, 2H), 3.44 (q, 2H), 4.10 (qt, 1H), 4.64 (s, 2H), 7.31-7.44 (m, 4H), 7.60 (dd, 1H), 7.72-7.83 (m, 5H), 7.99 (d, 1H), 8.47 (t, 1H), 8.57 (s, 1H), 12.10 (brd s, 1H).

10 MS (APCI, pos): 532.3, 531.2, 530.2, 362.3, 361.2.

EXAMPLE 103 (general procedure (G))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(2,6-dichloropyridin-4-yl)ureidomethyl]benzoylamino}-propionic acid

15

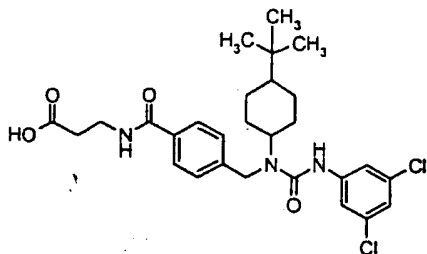
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.81 (s, 9H), 0.91 (m, 1H), 1.07 (m, 2H), 1.39 (m, 2H), 1.63-1.74 (m, 4H), 2.49 (t, 2H), 3.44 (q, 2H), 4.10 (t, 1H), 4.61 (s, 2H), 7.29 (d, 2H), 7.66 (s, 2H), 7.76 (d, 2H), 8.47 (t, 1H), 9.21 (s, 1H), 12.10 (brd s, 1H).

20

MS (APCI, pos): 549.2, 362.2, 361.2.

EXAMPLE 104 (general procedure (G))

3-[4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino]propionic acid



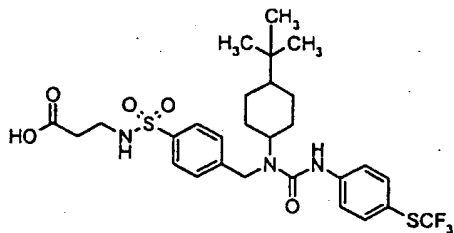
5

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.82 (s, 9H), 0.90 (m, 1H), 1.05-1.15 (m, 2H), 1.40 (m, 2H), 1.65-1.75 (m, 4H), 2.51 (t, 2H), 3.44 (q, 2H), 4.00 (m, 1H), 4.59 (s, 2H), 7.12 (t, 1H), 7.30 (d, 2H), 7.62 (d, 2H), 7.75 (d, 2H), 8.45 (t, 1H), 8.69 (s, 1H), 12.50 (brd s, 1H).

10 MS (APCI, pos): 552.2, 550.2, 549.2, 548.2, 362.3, 361.2.

EXAMPLE 105 (general procedure (G))

3-[4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]benzenesulfonylamino]propionic acid



15

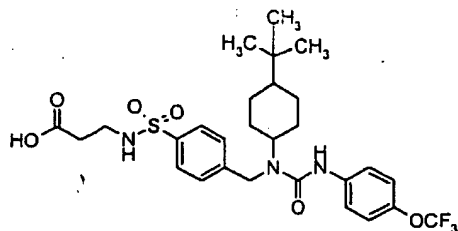
$^1\text{H}$  NMR (Acetone- $d_6$ ):  $\delta$  0.83 (s, 9H), 0.97 (m, 1H), 1.17 (q, 2H), 1.54 (q, 2H), 1.81 (m, 4H), 2.50 (t, 2H), 3.15 (t, 2H), 4.17 (t, 1H), 4.76 (s, 2H), 6.60 (brd s, 1H), 7.56 (m, 4H), 7.67 (d, 2H), 7.83 (d, 2H), 8.19 (s, 1H).

20

MS (APCI, pos): 617.2, 616.2, 399.2, 398.1, 397.2.

**EXAMPLE 106 (general procedure (G))**

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzenesulfonyl-amino}propionic acid



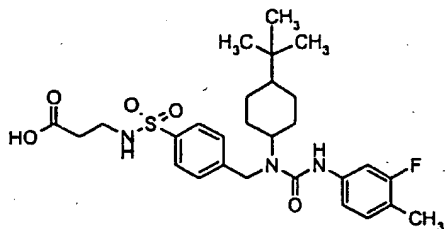
5

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.82 (s, 9H), 1.11-1.17 (m, 3H), 1.49 (q, 2H), 1.70 (t, 4H), 2.32 (t, 2H), 2.90 (t, 2H), 4.01 (m, 2H), 4.62 (s, 2H), 7.22 (d, 2H), 7.45 (d, 2H), 7.55 (d, 2H), 7.72 (d, 2H), 8.59 (s, 1H), 12.20 (brd s, 1H).

10 MS (APCI, pos): 601.3, 600.2, 399.2, 398.3, 397.2.

**EXAMPLE 107 (general procedure (G))**

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-fluoro-4-methylphenyl)ureidomethyl]benzenesulfonyl-amino}propionic acid

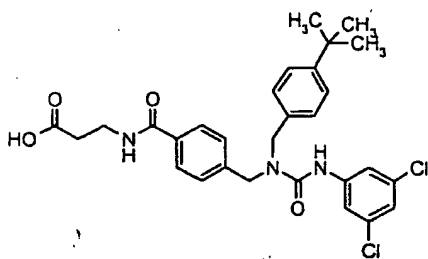


15

$^1\text{H}$  NMR (Acetone- $d_6$ ):  $\delta$  0.82 (s, 6H), 0.84 (s, 3H), 1.21 (m 1H), 1.43-1.59 (m, 5H), 1.79-1.92 (m, 3H), 2.16 (s, 3H), 2.52 (t, 2H), 3.14 (q, 2H), 4.36 (m, 1H), 4.85 (s, 2H), 6.51 (btd t, 1H), 7.07 (d, 2H), 7.49-7.57 (m, 3H), 7.83-7.90 (m, 3H), 11.50 (brd s, 1H).

20

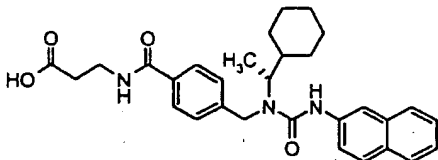
MS (APCI, pos): 548.2, 399.1, 398.3, 397.2.

EXAMPLE 108 (general procedure (G))3-{4-[1-(4-*tert*-Butylbenzyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}propionic acid

5 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.25 (s, 9H), 3.33 (m, 2H), 3.43 (m, 2H), 4.51 (s, 2H), 4.63 (s, 2H), 7.14-7.17 (m, 3H), 7.30 (d, 2H), 7.36 (d, 2H), 7.66 (m, 2H), 7.79 (s, 1H), 8.50 (t, 1H), 8.97 (s, 1H), 12.25 (brd s, 1H).

MS (APCI, pos): 558.2, 557.2, 556.2, 370.1, 369.1.

10

EXAMPLE 109 (general procedure (G))3-{4-[1-((1*R*)-1-Cyclohexylethyl)-3-naphthalene-2-ylureidomethyl]benzoylamino}propionic acid

15

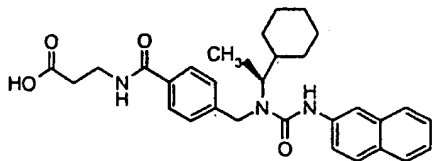
<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.92-1.10 (m, 8H), 1.36 (q, 1H), 1.59 (m, 2H), 1.67 (d, 3H), 2.51 (t, 2H), 3.54 (q, 2H), 4.05 (m, 1H), 4.30 (d, 2H), 4.50 (d, 2H), 6.32 (brd s, 2H), 6.47 (brd s, 1H), 7.00-7.07 (m, 2H), 7.23 (t, 1H), 7.27-7.30 (m, 3H), 7.54-7.67 (m, 6H).

20 MS (APCI, pos): 503.3, 502.3, 333.3.



EXAMPLE 110 (general procedure (G))

3-[4-[1-((1S)-1-Cyclohexylethyl)-3-naphthalene-2-ylureidomethyl]benzoylamino]propionic acid



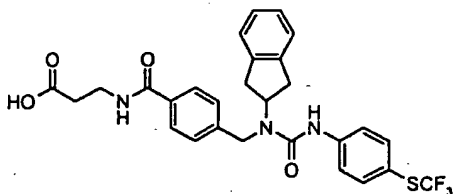
5

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.91 (m, 3H), 1.09 (d, 3H), 1.11 (m, 3H), 1.15-1.88 (m, 6H), 2.44 (t, 2H), 3.34 (q, 2H), 4.09 (q, 1H), 4.36 (d, 1H), 4.80 (d, 1H), 7.32 (t, 1H), 7.38 (d, 2H), 7.42 (t, 1H), 7.55 (dd, 1H), 7.71-7.79 (m, 5H), 7.97 (dd, 1H), 8.52 (t, 1H).

10 MS (APCI, pos): 502.2, 353.0.

EXAMPLE 111 (general procedure (G))

3-[4-[1-(2,3-Dihydro-1H-inden-2-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino]-propionic acid

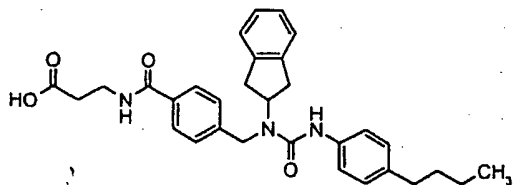


15

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  2.44 (t, 2H), 2.90-3.06 (m, 4H), 3.40-3.46 (m, 2H), 4.67 (s, 2H), 5.09 (qt, 1H), 7.06-7.21 (m, 4H), 7.29 (d, 2H), 7.52 (d, 2H), 7.68 (d, 2H), 7.77 (d, 2H), 8.48 (t, 1H), 8.88 (s, 1H), 12.00 (brd s, 1H).

20

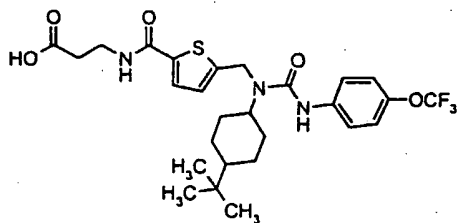
MS (APCI, pos): 558.2, 339.1.

EXAMPLE 112 (general procedure (G))3-[4-[1-(2,3-Dihydro-1H-inden-2-yl)-3-(4-butylphenyl)ureidomethyl]benzoylamino]propionic acid

5

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.87 (t, 3H), 1.28 (hex, 2H), 1.49 (qt, 2H), 2.51 (t, 2H), 2.69 (t, 2H), 2.95 (d, 1H), 3.01 (d, 1H), 3.25 (d, 1H), 3.30 (d, 1H), 3.70 (q, 2H), 4.59 (s, 2H), 5.21 (qt, 1H), 6.21 (s, 1H), 6.91 (t, 1H), 7.02 (s, 4H), 7.18 (s, 4H), 7.37 (d, 2H), 7.47 (d, 2H).

10 MS (APCI, pos): 514.2, 339.1.

EXAMPLE 113 (general procedure (G))3-[5-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]thiophene-2-carbonylamino]propionic acid

15

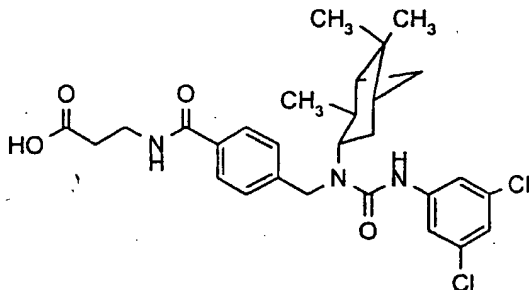
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.61 (s, 9H), 0.73 (m, 1H), 0.87 (q, 2H), 1.24 (q, 2H), 1.51 (m, 4H), 2.21 (t, 2H), 3.16 (q, 2H), 3.73 (t, 1H), 4.42 (s, 2H), 6.77 (d, 1H), 7.02 (d, 2H), 7.29 (d, 2H), 7.33 (d, 1H), 8.21 (t, 1H), 8.37 (s, 1H), 11.99 (brd s, 1H).

20

MS (APCI, neg): 568.0, 569.0:

EXAMPLE 114 (general procedure (G))

3-{4-[1-((2R,3R)-2,6,6-Trimethylbicyclo[3.3.1]hept-3-yl)-3-(3,5-dichlorophenyl)ureidomethyl]-benzoylamino}propionic acid



5

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  0.96 (d, 3H), 1.07 (s, 3H), 1.18 (s, 3H), 1.65-1.71 (m, 2H), 1.89-1.94 (m, 2H), 2.20-2.28 (m, 2H), 2.44 (t, 2H), 3.49 (q, 2H), 4.66 (s, 2H), 4.85 (m, 1H), 7.10 (t, 1H), 7.30 (d, 2H), 7.53 (d, 2H), 7.80 (d, 2H), 8.47 (t, 1H), 8.69 (s, 1H).

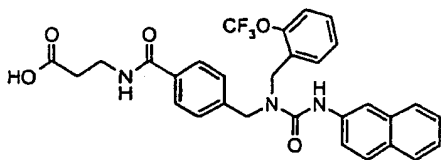
10 MS (APCI, pos): 546.1, 359.2, 287.1.

The following examples 115 to 136 were all found to displace more than 50% of the glucagon tracer when screened at 1  $\mu\text{M}$  concentration in the glucagon binding assay II. These compounds are all expected to be present in the library.

15

EXAMPLE 115 (general procedure (G))

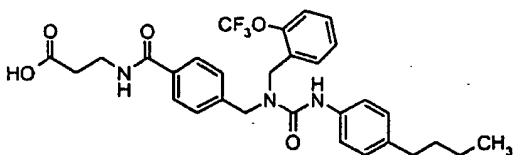
3-{4-[1-(2-Trifluoromethoxybenzyl)-3-naphthalene-2ylureidomethyl]benzoylamino}propionic acid



5

EXAMPLE 116 (general procedure (G))

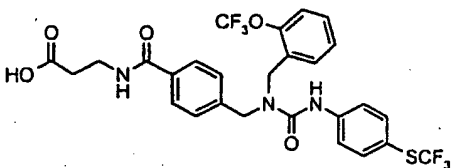
3-{4-[1-(2-Trifluoromethoxybenzyl)-3-(4-butylphenyl)ureidomethyl]benzoylamino}propionic acid



10

EXAMPLE 117 (general procedure (G))

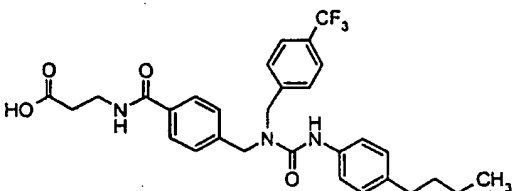
3-{4-[1-(2-Trifluoromethoxybenzyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]benzoylamino}propionic acid



15

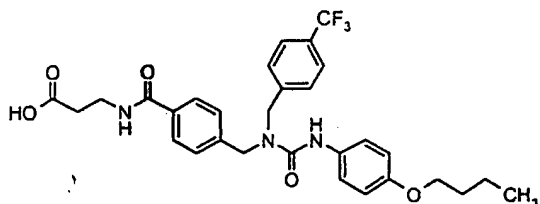
EXAMPLE 118 (general procedure (G))

3-{4-[1-(4-Trifluoromethylbenzyl)-3-(4-butylphenyl)ureidomethyl]benzoylamino}propionic acid



EXAMPLE 119 (general procedure (G))

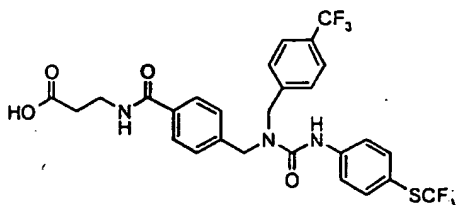
3-{4-[1-(4-Trifluoromethylbenzyl)-3-(4-butoxyphenyl)ureidomethyl]benzoylamino}propionic acid



5

EXAMPLE 120 (general procedure (G))

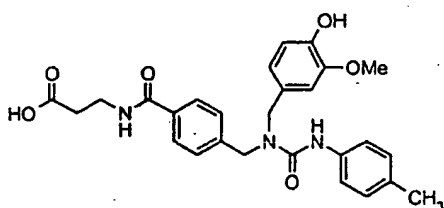
3-{4-[1-(4-Trifluoromethylbenzyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]benzoylamino}propionic acid



10

EXAMPLE 121 (general procedure (G))

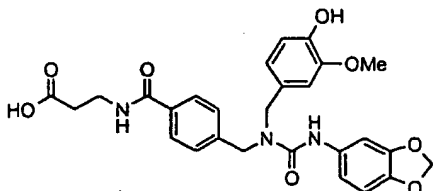
3-{4-[1-(4-Hydroxy-3-methoxybenzyl)-3-(4-methylphenyl)ureidomethyl]benzoylamino}propionic acid



15

EXAMPLE 122 (general procedure (G))

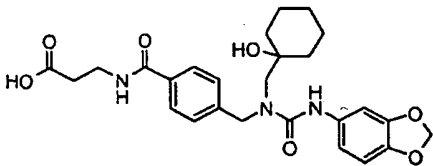
3-{4-[1-(4-Hydroxy-3-methoxybenzyl)-3-(3,4-methylenedioxyphenyl)ureidomethyl]benzoylamino}propionic acid



20

EXAMPLE 123 (general procedure (G))

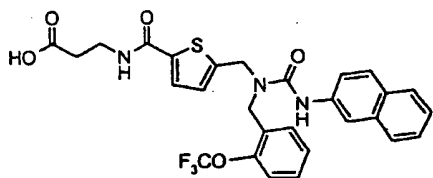
3-{4-[1-(1-Hydroxycyclohexylmethyl)-3-(3,4-methylenedioxyphenyl)ureidomethyl]benzoyl-  
amino}propionic acid



5

EXAMPLE 124 (general procedure (G))

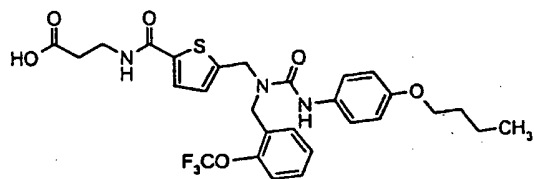
3-{5-[1-(2-Trifluoromethoxybenzyl)-3-naphthalene-2-ylureidomethyl]thiophene-2-carbonyl-  
amino}propionic acid



10

EXAMPLE 125 (general procedure (G))

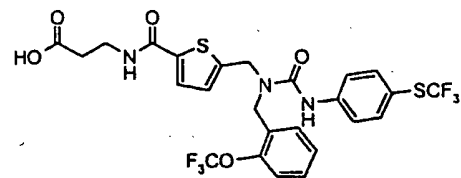
3-{5-[1-(2-Trifluoromethoxybenzyl)-3-(4-butoxyphenyl)ureidomethyl]thiophene-2-carbonyl-  
amino}propionic acid



15

EXAMPLE 126 (general procedure (G))

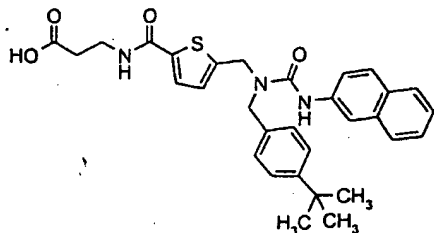
3-{5-[1-(2-Trifluoromethoxybenzyl)-3-(4-trifluoromethylsulfonylphenyl)ureidomethyl]-  
thiophene-2-carboxylamino}propionic acid



20

EXAMPLE 127 (general procedure (G))

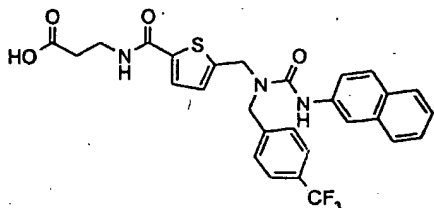
3-{5-[1-(4-*tert*-Butylbenzyl)-3-naphthalene-2-ylureidomethyl]thiophene-2-carbonylamino}-propionic acid



5

EXAMPLE 128 (general procedure (G))

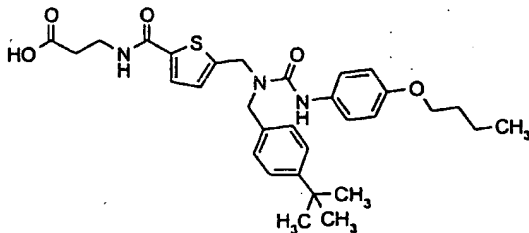
3-{5-[1-(4-Trifluoromethylbenzyl)-3-naphthalene-2-ylureidomethyl]thiophene-2-carbonylamino}propionic acid



10

EXAMPLE 129 (general procedure (G))

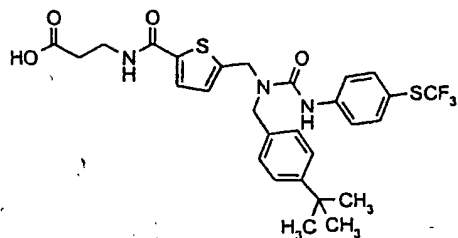
3-{5-[1-(4-*tert*-Butylbenzyl)-3-(4-butoxyphenyl)ureidomethyl]thiophene-2-carbonylamino}-propionic acid



15

EXAMPLE 130 (general procedure (G))

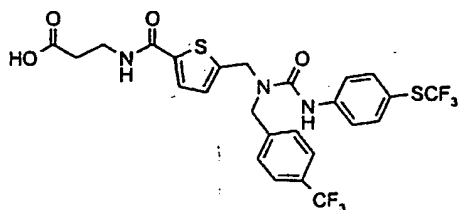
3-{5-[1-(4-*tert*-Butylbenzyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]thiophene-2-carbonylamino}propionic acid



5

EXAMPLE 131 (general procedure (G))

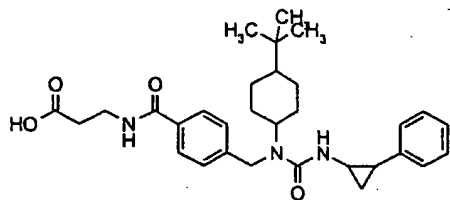
3-{5-[1-(4-Trifluoromethylbenzyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]thiophene-2-carbonylamino}propionic acid



10

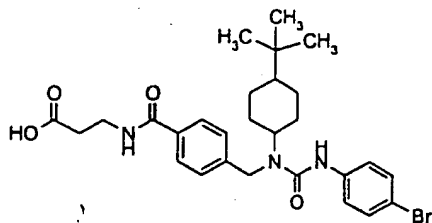
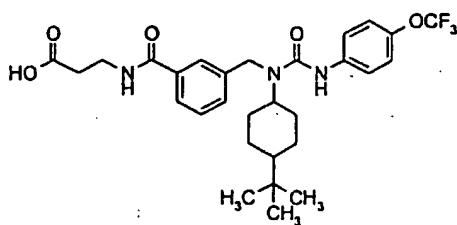
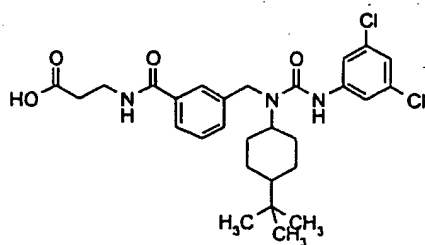
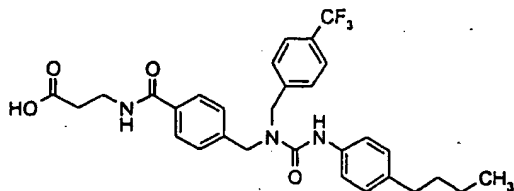
EXAMPLE 132 (general procedure (G))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(2-phenylcyclopropyl)ureidomethyl]benzoylamino}propionic acid



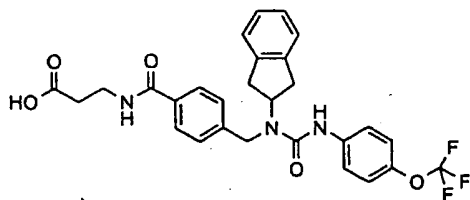
15



**EXAMPLE 133 (general procedure (G))****3-{4-[3-(4-Bromophenyl)-1-(4-*tert*-butylcyclohexyl)ureidomethyl]benzoylamino}propionic acid****5 EXAMPLE 134 (general procedure (G))****3-{3-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid****10 EXAMPLE 135 (general procedure (G))****3-{3-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}propionic acid****15 EXAMPLE 136 (general procedure (G))****3-{4-[3-(4-Butylphenyl)-1-(4-trifluoromethylbenzyl)ureidomethyl]benzoylamino}propionic acid**

EXAMPLE 137 (general procedure (G))

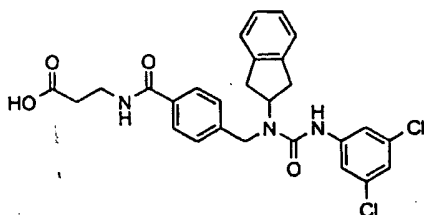
3-{4-[1-(1-Indan-2-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



- 5  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  2.52 (t, 2H), 2.97 (m, 4H), 3.47 (qt, 2H), 4.72 (s, 2H), 7.09 – 7.20 (m, 4H), 7.24 (d, 2H), 7.29 (d, 2H), 7.57 (d, 2H), 7.77 (d, 2H), 8.48 (brd t, 1H), 8.73 (brd s, 1H), 12.21 (brd s, 1H).

MS (APCI, pos): 542.2, 543.2, 339.1.

10

EXAMPLE 138 (general procedure (G))3-{4-[1-(1-Indan-2-yl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}propionic acid

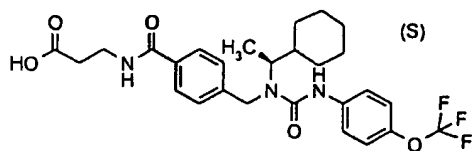
- 15  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  2.51 (t, 2H), 2.95 – 2.99 (m, 4H), 3.45 (qt, 2H), 4.71 (s, 2H), 7.09 – 7.18 (m 5H), 7.28 (d, 2H), 7.64 (s, 2H), 7.78 (d, 2H), 8.49 (t, 1H), 8.86 (s, 1H), 12.21 (brd s, 1H).

MS (APCI, pos): 526.1, 339.1.

20

EXAMPLE 139 (general procedure (G))

3-[4-[1-((1S)-1-Cyclohexylethyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino]-propionic acid



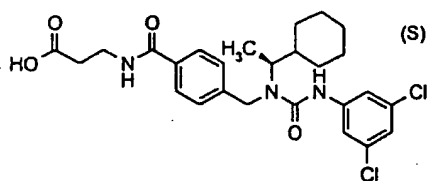
5

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  0.84 – 1.19 (m, 8H), 1.47 – 1.70 (m, 6H), 1.88 (t, 2H), 3.16 (qt, 2H), 4.03 (quintet, 1H), 4.33 (d, 1H), 4.78 (d, 1H), 7.10 (d, 2H), 7.50 (d, 2H), 7.70 (d, 2H), 8.62 (brd s, 1H), 8.95 (brd t, 1H).

10 MS (APCI, pos): 536.2, 537.2, 538.2.

EXAMPLE 140 (general procedure (G))

3-[4-[1-((1S)-1-Cyclohexylethyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino]propionic acid



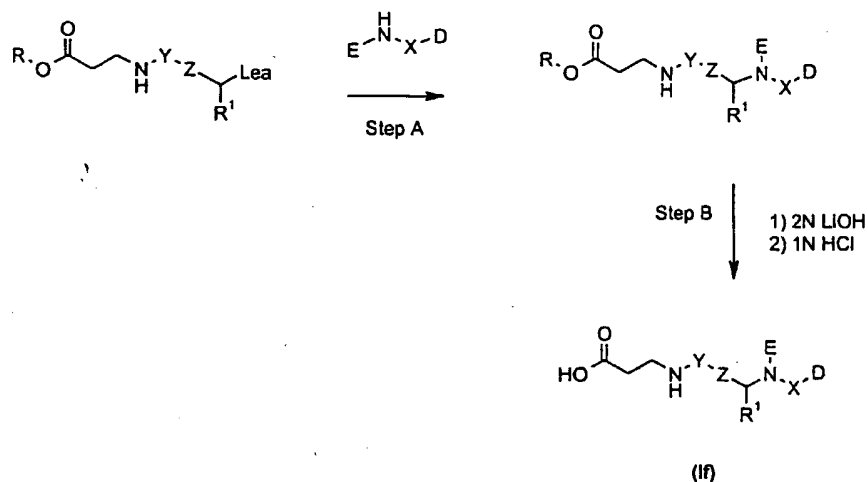
15

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.16 – 1.27 (m, 8H), 1.40 (m, 1H), 1.69 – 1.80 (m, 5H), 2.68 (t, 2H), 3.70 (qt, 2H), 4.20 (m, 1H), 4.43 (dd, 2H), 6.44 (brd s, 1H), 6.94 (m, 2H), 7.17 (s, 2H), 7.36 (d, 2H), 7.74 (d, 2H).

20

MS (APCI, pos): 520.2, 522.1, 333.2.

General procedure (H) for the solution phase synthesis of compounds of the general formula (If):



5

wherein

$R^1$ , E, Z and D are as defined for formula (I),

10 X is  $-(CH_2)_q-$ , wherein q is as defined for formula (I),

Y is  $-C(O)-$  or  $-S(O)_2-$ ,

R is  $C_{1-6}$ -alkyl and

15

Lea is a leaving group such as chloro, bromo, iodo, mesyl or tosyl.

The preparation of starting materials are as described above in procedure (G).

20 Library solution phase synthesis (procedure (H)) of compounds of the general formula (If):

Step A:

The appropriate alkylhalide (0.02 mmol) in DMF was added into the wells of a deepwell plate containing the appropriate amine (E-NH-X-D) (0.02 mmol) and solid potassium carbonate (2 eq) in DMF. The mixtures were agitated at 55°C for 16 hours to give the alkylated product.

25

Step B:

To the crude product from step A was added aqueous 2M LiOH (4 eq). The mixtures are agitated for at least four hours before they are filtered. Aqueous 1 N HCl was then added to give the desired carboxylic acids.

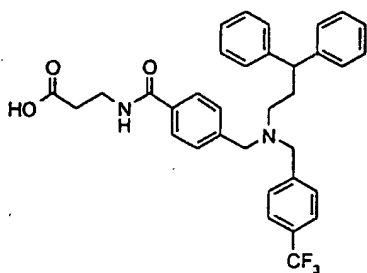
5

The following examples 141 to 152 were prepared according to the general procedure (H). They were all found to displace more than 50% of the glucagon tracer when screened at 1  $\mu$ M concentration in the glucagon binding assay II. The compounds are all expected to be present in the library.

10

EXAMPLE 141 (general procedure (H))

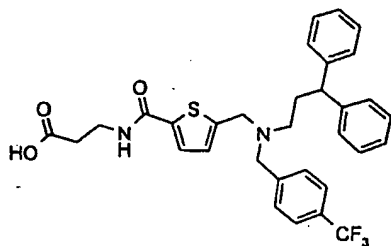
3-(4-(((3,3-Diphenylpropyl)-(4-trifluoromethylbenzyl)amino)methyl)benzoylamino)propionic acid



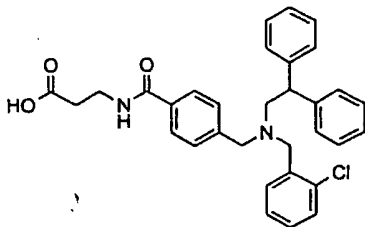
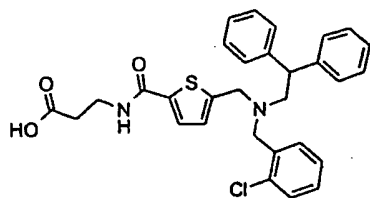
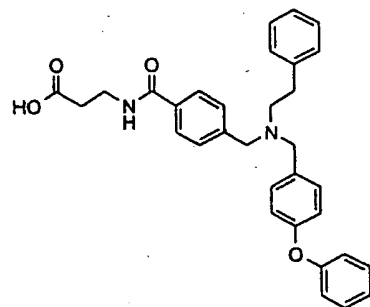
15

EXAMPLE 142 (general procedure (H))

3-(5-(((3,3-Diphenylpropyl)-(4-trifluoromethylbenzyl)amino)methyl)thiophene-2-carbonylamino)propionic acid

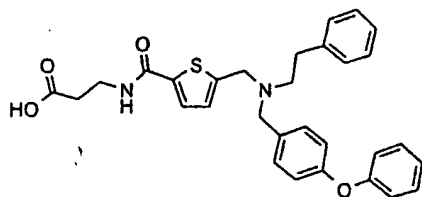


20

EXAMPLE 143 (general procedure (H))3-(4-(((2,2-Diphenylethyl)-(2-chlorobenzyl)amino)methyl)benzoylamino)propionic acid5 EXAMPLE 144 (general procedure (H))3-(5-(((2,2-Diphenylethyl)-(2-chlorobenzyl)amino)methyl)thiophene-2-carbonylamino)-propionic acid10 EXAMPLE 145 (general procedure (H))3-(4-(((2-Phenylethyl)-(4-phenoxybenzyl)amino)methyl)benzoylamino)propionic acid

EXAMPLE 146 (general procedure (H))

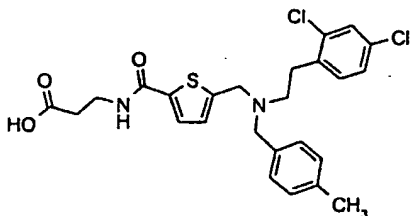
3-(5-[(2-Phenylethyl)-(4-phenoxybenzyl)amino]methyl)thiophene-2-carboxylamino)propionic acid



5

EXAMPLE 147 (general procedure (H))

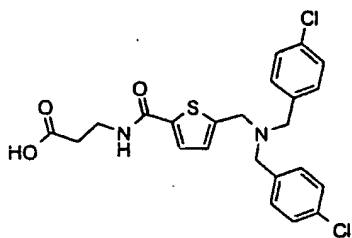
3-(5-[(2,4-Dichlorophenethyl)-(4-methylbenzyl)amino]methyl)thiophene-2-carboxylamino)-propionic acid

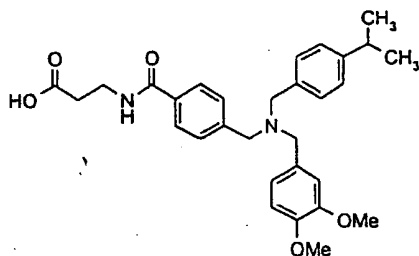


10

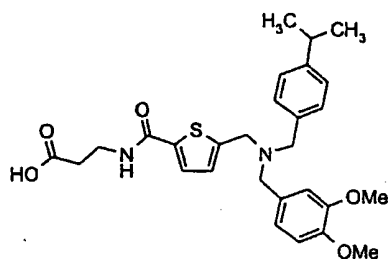
EXAMPLE 148 (general procedure (H))

3-(5-[(Bis-(4-chlorobenzyl)amino]methyl)thiophene-2-carboxylamino)propionic acid

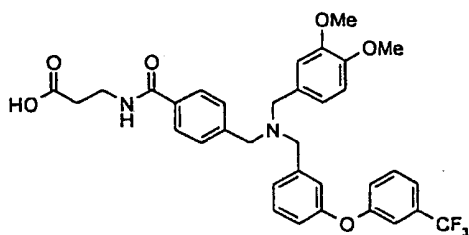


EXAMPLE 149 (general procedure (H))3-(4-((3,4-Dimethoxybenzyl)-(4-isopropylbenzyl)amino)methyl)benzoylamino)propionic acid

5

EXAMPLE 150 (general procedure (H))3-(5-((3,4-Dimethoxybenzyl)-(4-isopropylbenzyl)amino)methyl)thiophene-2-carbonylamino)-propionic acid

10

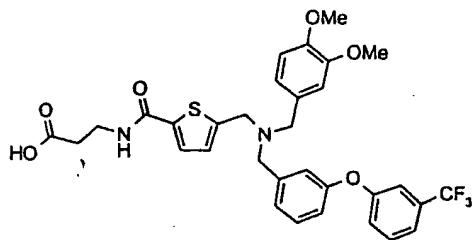
EXAMPLE 151 (general procedure (H))3-(4-((3,4-Dimethoxybenzyl)-(3-(3-trifluoromethylphenoxy)benzyl)amino)methyl)benzoylamino)propionic acid

15



EXAMPLE 152 (general procedure (H))

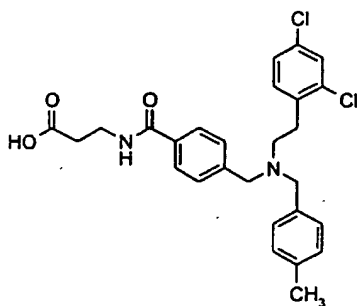
3-(5-(((3,4-Dimethoxybenzyl)-(3-[3-trifluoromethoxy]phenoxy]benzyl)amino)methyl}thiophene-2-carboxylamino)propionic acid



5

EXAMPLE 153 (general procedure (H))

3-(4-(((2,4-Dichlorophenethyl)-(4-methylbenzyl)amino)methyl)benzoylamino)propionic acid

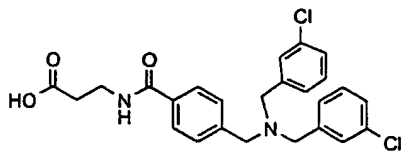


- 10  $^1\text{H NMR}$  (MeOH- $d_4$ ):  $\delta$  2.38 (s, 3H), 2.64 (t, 2H), 3.10 (m, 4H), 3.50 (qt, 2H), 4.40 (s, 2H), 4.50 (s, 2H), 7.20 (m, 4H), 7.40 (m, 3H), 7.50 (d, 2H), 7.90 (d, 2H), 8.60 (t, 1H).

MS (APCI, pos): 499.1, 500.2, 501.2.

15 EXAMPLE 154 (general procedure (H))

3-(4-([Bis-(3-chlorobenzyl)amino]methyl)benzoylamino)propionic acid

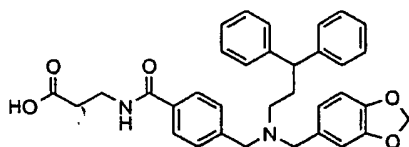


- 20  $^1\text{H NMR}$  (CDCl<sub>3</sub>):  $\delta$  2.70 (t, 2H), 3.40 (s, 4H), 3.50 (s, 2H), 3.70 (qt, 2H), 6.9 (t, 1H), 7.20 (m, 6H), 7.30 (s, 2H), 7.40 (d, 2H), 7.70 (d, 2H).

MS (APCI, pos): 471.0, 472.0, 473.0.

**EXAMPLE 155 (general procedure (H))**

3-(4-((3,3-Diphenylpropyl)-(3,4-methylenedioxybenzyl)amino)methyl)benzoylamino)propionic acid

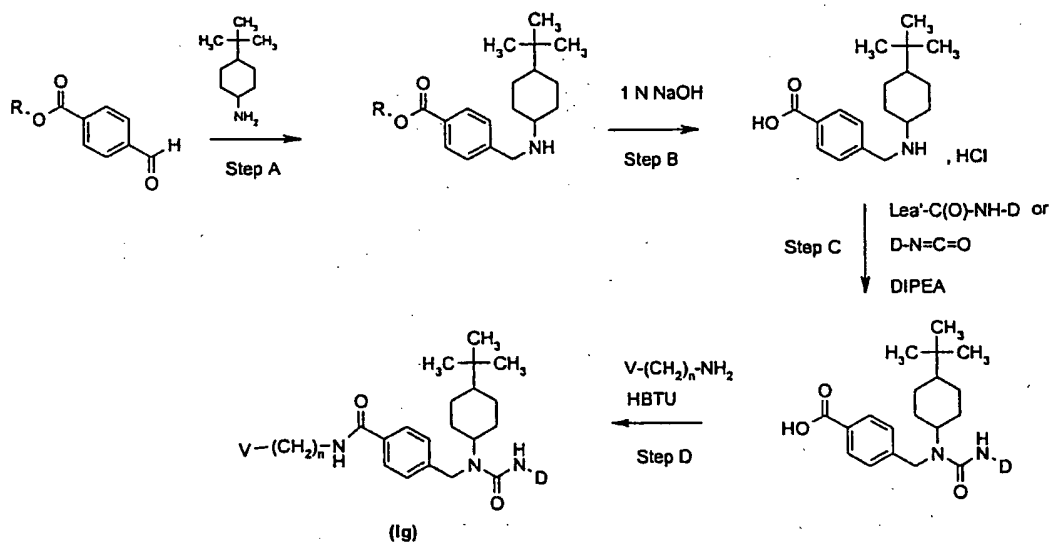


$^1\text{H}$  NMR ( $\text{CD}_3\text{CN}$ ):  $\delta$  2.46 – 2.54 (m, 2H), 2.63 (t, 2H), 2.82 – 2.88 (m, 2H), 3.61 (qt, 2H), 3.86 (t, 1H), 4.20 – 4.40 (m, 4H), 6.02 (s, 2H), 6.83 (d, 1H), 6.90 (d, 1H), 6.97 (s, 1H), 7.16 – 7.29 (m, 10H), 7.50 (d, 2H), 7.77 (d, 2H).

MS (APCI, pos): 551.2, 552.2, 553.2.

General procedure (I) for the solution phase synthesis of compounds of the general formula

(Ig):



wherein

n, D and V are as defined for formula (I),

R is C<sub>1-6</sub>-alkyl and

Lea' is a leaving group such as -OSu, chloro, phenoxy or 4-nitrophenoxy.

5    Step A:

To a solution of ethyl 4-formylbenzoate (6 g, 33.7 mmol) in DMF was added 4-*tert*-butylcyclohexylamine (5.8 g, 37.1 mmol), sodium cyanoborohydride (3.2 g, 50.6 mmol) and a catalytic amount of TFA. The solution was stirred at room temperature for 5 hours. The reaction was diluted with ethyl acetate and washed with aqueous sodium bicarbonate (3x), brine (3x),  
10    dried over MgSO<sub>4</sub>, and concentrated to a syrup. The desired secondary amine was purified by silica gel column chromatography using ethyl acetate.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.78 (s, 9H), 0.91 (brd m, 5H), 1.30 (t, 3H), 1.67 (brd m, 2H), 1.93 (brd m, 2H), 2.21 (1H), 3.77 (s, 2H), 4.30 (qt, 2H), 7.44 (d, 2H), 7.87 (d, 2H).

15

Step B:

To a solution of the above benzoate in THF/MeOH (3/1) was added aqueous 1M NaOH. After stirring the reaction at room temperature for 15 minutes, the solution was made acidic with 1N HCl. The product was extracted with ethyl acetate (3x) and washed with brine (3x),  
20    dried over MgSO<sub>4</sub>, and concentrated to a solid. The carboxylic acid product was recrystallized from dichloromethane as the hydrochloride salt.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.82 (s, 9H), 0.97 (m, 3H), 1.44 (qt, 2H), 1.81 (m, 2H), 2.17 (m, 2H), 2.90 (brd m, 1H), 4.20 (t, 2H), 7.73 (d, 2H), 7.95 (d, 2H), 9.52 (s, 2H), 12.60 (brd s, 1H).

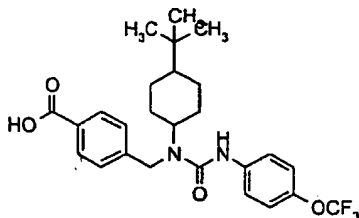
25

Step C:

To a solution of the amine in DMF was added the desired isocyanate (1.1 eq) or alternatively Lea'-C(O)-NH-D, and the reaction was stirred at room temperature for 10 minutes. When using Lea'-C(O)-NH-D a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any tertiary amine or potassium carbonate was also added. The solvent was concentrated to an oil. The residue was suspended in ethyl acetate and upon sitting in cold, the  
30    desired urea crystallized as a white solid.

Examples of products prepared in this fashion are shown below.

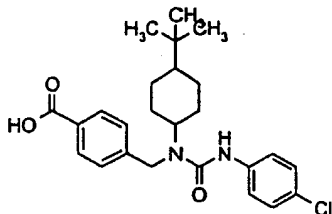
4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid



5

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.81 (brd s, 9H), 1.12 (qt, 2H), 1.37 (qt, 2H), 1.69 (t, 4H), 4.06 (t, 1H), 4.62 (s, 2H), 7.21 (d, 2H), 7.35 (d, 2H), 7.54 (d, 2H), 7.87 (d, 2H), 8.57 (s, 1H), 12.84 (brd s, 1H).

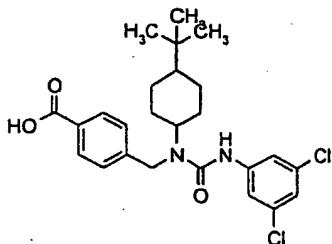
10 4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]benzoic acid



$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.82 (s, 9H), 0.91 (m, 1H), 1.15 (qt, 2H), 1.37 (qt, 2H), 1.69 (t, 4H), 4.04 (m, 1H), 4.61 (s, 2H), 7.26 (d, 2H), 7.35 (d, 2H), 7.47 (d, 2H), 7.86 (d, 2H), 8.49 (s, 1H), 12.83 (brd s, 1H).

15

4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoic acid



20  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.81 (s, 9H), 0.92 (m, 1H), 1.14 (qt, 2H), 1.47 (qt, 2H), 1.69-1.72 (m, 4H), 4.04 (m, 1H), 4.61 (s, 2H), 7.12 t, 1H), 7.35 (d, 2H), 7.63 (d, 2H), 7.88 (d, 2H), 8.87 (s, 1H), 12.95 (brd s, 1H).

Step D:

This step was carried out in a combinatorial fashion in solution.

- 5 To a solution of one of the above benzoic acids (0.02 mmol) in a suitable solvent such as  $\text{CH}_2\text{Cl}_2$ , DMF, or THF was added diisopropylethylamine (3 eq) and HBTU (1.1 eq). The reaction was allowed to stir for 30 minutes before the amine (1.1 eq) was added. The solution was stirred at room temperature for 4 hours. The solvents were evaporated under reduced pressure to afford the crude product.

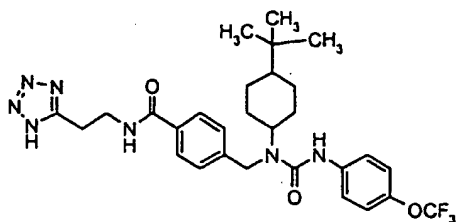
10

The following examples were prepared according to the general procedure (I).

EXAMPLE 156 (general procedure (I))

4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-[2-(1*H*-tetrazol-5-yl)ethyl]benzamide

15



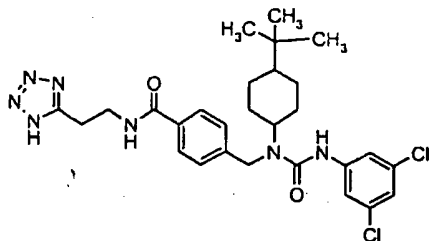
- $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  0.81 (s, 9H), 0.90 (m, 1H), 1.11 (qt, 2H), 1.41 (qt, 2H), 1.70 (m, 4H), 3.13 (t, 2H), 3.60 (qt, 2H), 4.05 (quintet, 1H), 4.60 (s, 2H), 7.22 (d, 2H), 7.31 (d, 2H), 7.55 (d, 2H), 7.73 (d, 2H), 8.54 (s, 1H), 8.56 (t, 1H).

20

MS (APCI, pos): 588.3.

EXAMPLE 157 (general procedure (I))

4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-N-[2-(1*H*-tetrazol-5-yl)ethyl]benzamide



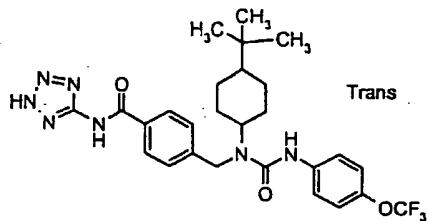
5

<sup>1</sup>H NMR (MeOH-*d*<sub>4</sub>): δ 0.87 (s, 9H), 1.01 (m, 1H), 1.25 (m, 2H), 1.46 (q, 2H), 1.83 (t, 4H), 3.27 (t, 2H), 3.78 (t, 2H), 4.10 (m, 1H), 4.67 (s, 2H), 7.04 (t, 1H), 7.38 (d, 2H), 7.43 (t, 2H), 7.75 (d, 2H), 8.44 (brd s, 1H).

10 MS (APCI, pos): 480.2, 478.2, 477.2, 435.1, 433.2, 290.1, 156.2.

EXAMPLE 158 (general procedure (I))

4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2*H*-tetrazol-5-yl)benzamide



15

<sup>1</sup>H NMR (MeOH-*d*<sub>4</sub>): δ 0.86 (s, 9H), 1.01 (m, 1H), 1.22 (qt, 2H), 1.48 (qt, 2H), 1.85 (m, 4H), 4.11 (m, 1H), 4.70 (s, 2H), 7.16 (d, 2H), 7.42 (d, 2H), 7.46 (d, 2H), 7.99 (d, 2H).

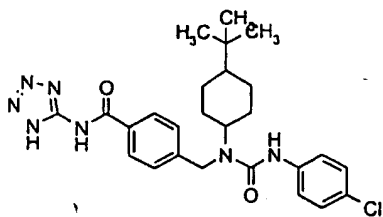
20 MS (APCI, pos): 560.2, 561.2, 357.1, 358.2.

The following examples 159 to 171 were all found to displace more than 50% of the glucagon tracer when screened at 1 μM concentration in the glucagon binding assay II. The compounds are all expected to be present in the library.

25

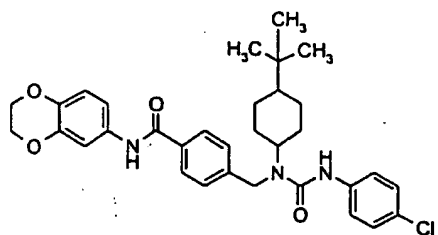
**EXAMPLE 159 (general procedure (I))**

4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]-*N*-(1*H*-tetrazol-5-yl)benzamide



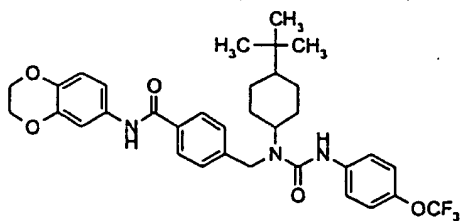
5 **EXAMPLE 160 (general procedure (I))**

4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]-*N*-(2,3-dihydro-1,4-benzodioxin-6-yl)benzamide



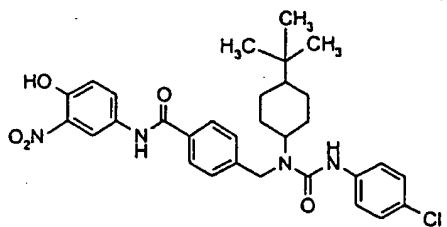
10 **EXAMPLE 161 (general procedure (I))**

4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-*N*-(2,3-dihydro-1,4-benzodioxin-6-yl)benzamide



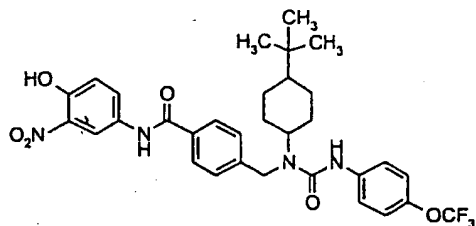
15 **EXAMPLE 162 (general procedure (I))**

4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]-*N*-(4-hydroxy-3-nitrophenyl)benzamide



EXAMPLE 163 (general procedure (I))

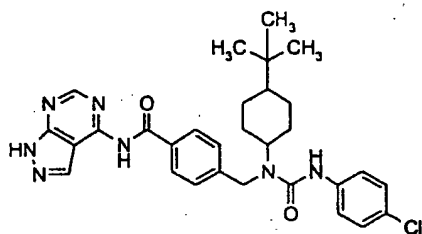
4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(4-hydroxy-3-nitrophenyl)benzamide



5

EXAMPLE 164 (general procedure (I))

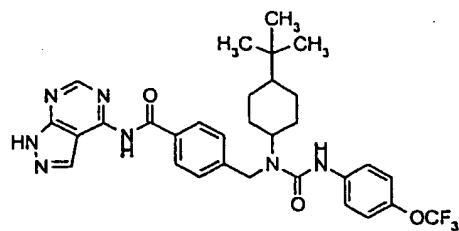
4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]-N-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)benzamide



10

EXAMPLE 165 (general procedure (I))

4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)benzamide

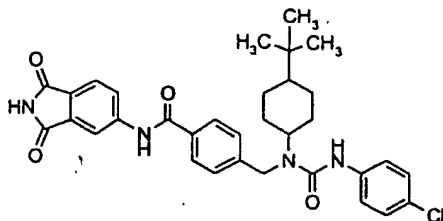


15



EXAMPLE 166 (general procedure (I))

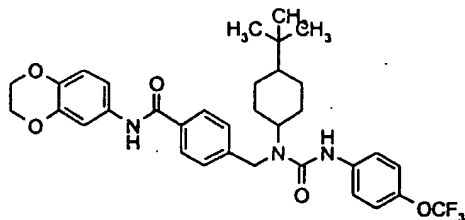
4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]-*N*-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)benzamide



5

EXAMPLE 167 (general procedure (I))

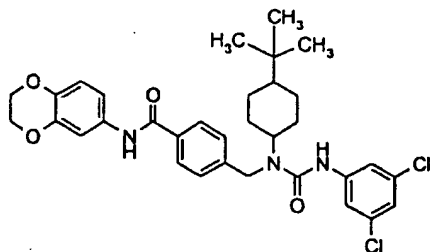
4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-*N*-(2,3-dihydro-1,4-benzodioxin-6-yl)benzamide



10

EXAMPLE 168 (general procedure (I))

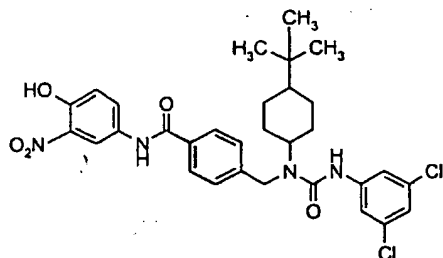
4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(2,3-dihydro-1,4-benzodioxin-6-yl)benzamide



15

**EXAMPLE 169 (general procedure (I))**

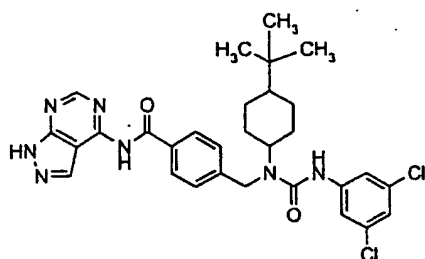
4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(4-hydroxy-3-nitrophenyl)-benzamide



5

**EXAMPLE 170 (general procedure (I))**

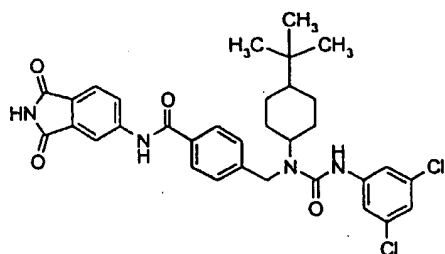
4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(1*H*-pyrazolo[3,4-*d*]-pyrimidin-4-yl)benzamide



10

**EXAMPLE 171 (general procedure (I))**

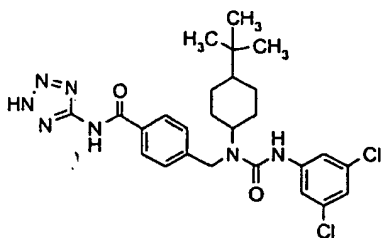
4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)benzamide



15

EXAMPLE 172 (general procedure (I))

4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-N-(2*H*-tetrazol-5-yl)-benzamide



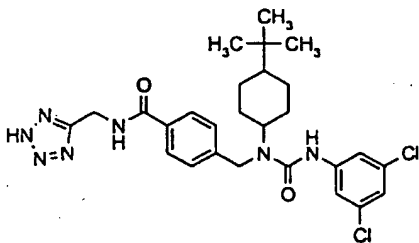
5

<sup>1</sup>H NMR (MeOH-*d*<sub>4</sub>): δ 0.92 (s, 9H), 1.01 (m, 1H), 1.18 – 1.31 (m, 2H), 1.44 – 1.52 (m, 2H), 1.80 – 1.87 (m, 4H), 4.12 (m, 1H), 4.72 (s, 2H), 7.05 (t, 1H), 7.46 (d, 2H), 7.49 (d, 2H), 8.02 (d, 2H).

10 MS (APCI, pos): 544.2, 357.2.

EXAMPLE 173 (general procedure (I))

4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-N-(2*H*-tetrazol-5-ylmethyl)-benzamide



15

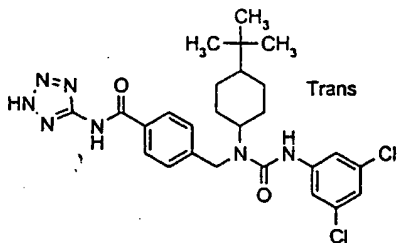
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.82 (s, 9H), 0.92 (d, 1H), 1.04 – 1.20 (m, 2H), 1.42 (qt, 2H), 1.70 (m, 4H), 4.05 (qt, 1H), 4.61 (s, 2H), 4.73 (d, 2H), 7.12 (s, 1H), 7.34 (d, 2H), 7.62 (s, 2H), 7.83 (d, 2H), 8.70 (s, 1H), 9.18 (t, 1H).

20

MS (APCI, pos): 558.2, 560.2, 372.2, 343.2.

**EXAMPLE 174 (general procedure (I))**

**4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide**



5

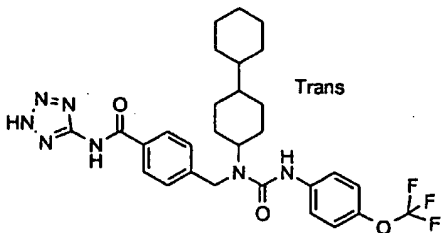
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.82 (s, 9H), 1.01 (m, 1H), 1.10 (m, 2H), 1.42 (m, 2H), 1.74 (m, 4H), 4.40 (m, 1H), 4.63 (s, 2H), 7.13 (s, 1H), 7.39 (d, 2H), 7.63 (s, 2H), 8.01 (d, 2H), 8.73 (s, 1H).

MS (APCI, neg): 542.1, 544.1.

10

**EXAMPLE 175 (general procedure (I))**

**4-[1-(*trans*-4-Cyclohexylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide**



15

*trans*-4-Cyclohexylcyclohexylamine was prepared according to H. Booth, G. C. Gidley, P. R. Thornburrow, J. Chem. Soc. B, 1971, 1047-50.

The *cis* isomer may be prepared by reductive amination of cyclohexylcyclohexyl ketone with the appropriate amine followed by column chromatographic separation of the *cis/trans* isomers.

20

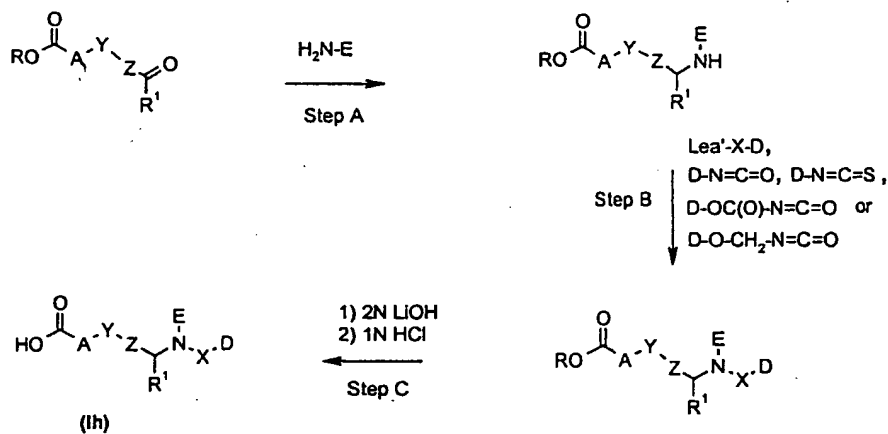
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.82 – 1.10 (m, 10H), 1.60 (m, 2H), 1.64 – 1.80 (m, 8H), 4.03 (quintet, 1H), 4.64 (s, 2H), 7.22 (d, 2H), 7.41 (d, 2H), 7.54 (d, 2H), 8.03 (d, 2H), 8.56 (s, 1H), 12.32 (s, 1H), 15.90 (brd s, 1H).

25

MS (APCI, pos): 586.1, 587.2, 383.2, 384.2.

General procedure (J) for the solution phase synthesis of compounds of the general formula (Ih):

5



wherein

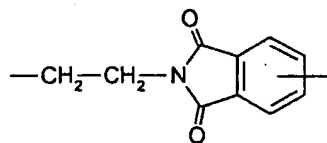
10  $R^1$ , E and D are as defined for formula (I),

X is  $-C(O)NH-$ ,  $-C(O)NH-CH_2-O-$ ,  $-C(O)NH-C(O)O-$  or  $-C(S)NH-$ ,

15  $-A-Y-$  is  $-(CH_2)_2-NH-C(O)-$  or  $-(CH_2)_n-O-$ , wherein n is as defined for formula (I), and Z is as defined for formula (I),

or

$-A-Y-Z-$  together is



20

R is  $C_{1-6}$ -alkyl and

$Lea'$  is a leaving group such as  $-OSu$ , chloro, phenoxy or 4-nitrophenoxy.

Step A:

The appropriate aldehyde (0.011 mmol) in  $\text{CH}_2\text{Cl}_2$  was dispensed into the wells of a deepwell plate containing the desired amines in  $\text{CH}_2\text{Cl}_2$ . To this solution was added sodium triacetoxy-  
5 borohydride (1.5 eq) followed by a catalytic amount of acetic acid. The reaction was left to proceed for 15 hours.

Step B:

To the resulting amines from step A was added the desired isocyanate or isothiocyanate or  
10 alternatively Lea'-X-D (0.011 mmol) in  $\text{CH}_2\text{Cl}_2$ . When using Lea'-X-D a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any tertiary amine or potassium carbonate was also added. The reactions were agitated for three hours and the solvents were removed under reduced pressure to give the desired ureas or thioureas.

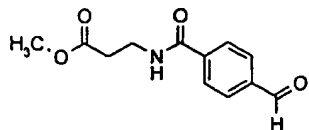
Step C:

The residue obtained in step B was dissolved in DMF and aqueous 2 M lithium hydroxide (10 eq.) was added into each reaction well. The samples were shaken overnight and filtered. Aqueous 1 N HCl was then added to give the desired carboxylic acids.

General preparation of formylarylcarboxamides as starting materials:

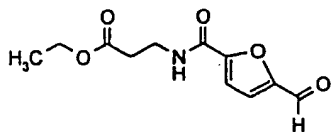
The formylarylcarboxamides were prepared from the coupling of the corresponding oxo-arylcarboxylic acid and the methyl or ethyl-3-aminopropionate hydrochloride according to the procedure described below.

25 To a solution of the formylarylcarboxylic acid in a suitable solvent such as  $\text{CH}_2\text{Cl}_2$ , DMF, or THF was added diisopropylethylamine (3 eq) and HBTU (1.1 eq). The reaction was allowed to stir for 30 minutes before ethyl or methyl-3-aminopropionate hydrochloride (1.1 eq) was added. The solution was stirred at room temperature for 4 hours. The solvents were evaporated under reduced pressure. The residue was taken up in ethyl acetate and 1N HCl. The  
30 organic layer was separated and washed with  $\text{H}_2\text{O}$  (2x), aqueous  $\text{NaHCO}_3$  (3x), brine (2x), dried over  $\text{MgSO}_4$  and concentrated to give the desired product.

Methyl 3-[(4-formylbenzoyl)amino]propionate:

5  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ ):  $\delta$  2.62 (t, 2H), 3.52 (q, 2H), 3.60 (s, 3 H), 8.00 (m, 4 H), 8.98 (t, 1 H), 10.06 (s, 1H).

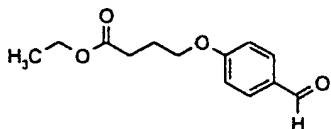
MS (APCI, neg.): 234.0, 147.9

Ethyl 3-[(5-formyl-2-furoyl)aminopropionate:

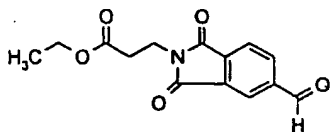
10

$^1\text{H NMR}$  ( $\text{DMSO}-d_6$ ):  $\delta$  1.67 (t, 3H), 2.57 (t, 2H), 3.48 (q, 2H), 4.08 (q, 2H), 7.29 (d, 1H), 7.59 (d, 1H), 8.83 (brd t, 1H), 9.69 (s, 1H).

15 MS (APCI, pos.): 240.1, 194.1, 152.0.

Ethyl 4-(4-formylphenoxy)butyrate:

20 This compound was prepared according to D. R. Buckle, A. E. Fenwick, D. J. Outred, C. J. M. Rockwell, J. Chem. Res. Miniprint 12 (1987) 3144-3177.

Ethyl 3-[5-formyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl]propionate:

25

Step 1: Ethyl 3-[5-methyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl]propionate

A solution of 4-methylphthalic anhydride (21.3 g, 0.13 mol), ethyl 3-aminopropionate hydrochloride (20.2 g, 0.13 mol), and triethylamine (19 mL) in NMP was stirred at ambient temperature for 3 days, and heated to 130°C for 3 hours. The mixture was diluted with water

5 (300 mL), and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with 1N hydrochloric acid (2 x 50 mL), sodium bicarbonate solution (2 x 50 mL), dried (MgSO<sub>4</sub>), and concentrated to give 27.3 g yellow oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.21 (t, 3H), 2.50 (s, 3H), 2.70 (t, 2H), 3.97 (t, 2H), 4.17 (q, 2H), 7.51 (d,  
10 1H), 7.64 (s, 1H), 7.71 (d, 1H).

MS (APCI, pos.): 262, 216.

Step 2: Ethyl 3-[5-bromomethyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl]propionate

15 The material from step 1 (27.3 g, 0.10 mol) was dissolved in carbon tetrachloride (50 mL), and *N*-bromosuccinimide (19.5 g, 0.11 mol) and AIBN (200 mg) was added. The mixture was refluxed for 5 hours, filtered by suction, and the filtrate was concentrated to give 35.4 g yellow oil.

20 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.23 (t, 3H), 2.50 (s, 3H), 2.72 (t, 2H), 4.00 (t, 2H), 4.13 (q, 2H), 4.55 (s, 2H), 7.71 (d, 1H), 7.82 (d, 1H), 7.87 (s, 1H).

MS (APCI, pos.): 340, 342.

25 Step 3: Ethyl 3-[5-formyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl]propionate

The crude material from step 2 was dissolved in DMSO (70 mL). Powdered K<sub>2</sub>HPO<sub>4</sub> (18 g, 0.10 mol) and KH<sub>2</sub>PO<sub>4</sub> (7 g, 0.05 mol) were added. The mixture was stirred at 80°C for 5 hours, diluted with water (500 mL), and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried (MgSO<sub>4</sub>), and concentrated. After column chromatography  
30 (hexane, ethyl acetate 3:1) 4.8 g of the title compound was obtained.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.23 (t, 3H), 2.75 (t, 2H), 4.04 (t, 2H), 4.13 (q, 2H), 8.03 (d, 1H), 8.26 (d, 1H), 8.35 (s, 1H), 10.17 (s, 1H).

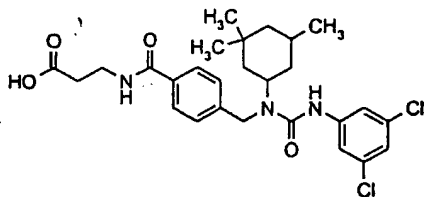
35 MS (APCI, neg.): 275.



The following examples were prepared according to the general procedure (J).

EXAMPLE 176 (general procedure (J))

- 5 3-[4-[3-(3,5-Dichlorophenyl)-1-(3,3,5-trimethylcyclohexyl)ureidomethyl]benzoylamino]-propionic acid

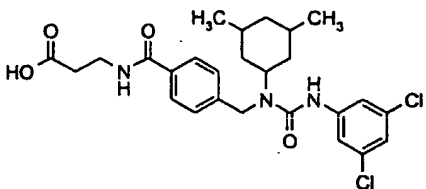


- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.14-1.29 (m, 5H), 1.33 - 1.37 (m, 1 H), 1.98 (brd, 1H), 2.49 (t, 2H),  
10 3.44 (q, 2H), 4.50 (m, 1H), 4.65 (d, 2H), 7.11 (t, 1H), 7.29 (d, 2H), 7.57 (s, 2H), 7.78 (d, 2H),  
8.85 (t, 1H), 8.62 (s, 1H), 12.21 (s, 1H).

MS (APCI, pos.): 536.2, 535.2, 534.2.

- 15 EXAMPLE 177 (general procedure (J))

3-[4-[3-(3,5-Dichlorophenyl)-1-(3,5-dimethylcyclohexyl)ureidomethyl]benzoylamino]propionic acid

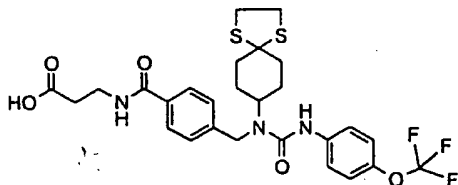


- 20 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.62 (q, 1H), 0.83 (d, 6H), 1.15 (m, 2H), 1.63 - 1.80 (m, 5H), 2.50 (t,  
2H), 3.37 (m, 2H), 4.45 (s, 1H), 4.78 (s, 2H), 7.11 (s, 1H), 7.26 (d, 2H), 7.59 (s, 2H), 7.77 (d,  
2H), 8.47 (t, 1H), 8.72 (s, 1H), 12.15 (brd, 1 H).

MS (APCI, pos.): 520.2

**EXAMPLE 178 (general procedure (J))**

3-{4-[1-(1,4-Dithiaspiro[4.5]dec-8-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl-  
amino}propionic acid



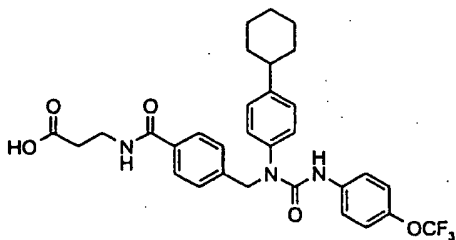
5

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.62 (m, 4 H), 2.03 (m, 4 H), 3.24 (m, 4 H), 3.40 (m, 2 H), 4.13 (m, 1 H), 4.57 (s, 2 H), 7.23 (d, 2 H), 7.32 (d, 2 H), 7.54 (d, 2 H), 7.76 (d, 2 H), 8.46 (t, 1 H), 8.57 (s, 1 H), 12.20 (brd, 1 H).

10 MS (APCI, pos.): 598.2.

**EXAMPLE 179 (general procedure (J))**

3-{4-[1-(4-Cyclohexylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-  
propionic acid



15

$^1\text{H}$  NMR (MeOH- $d_4$ ):  $\delta$  1.28 – 1.48 (m, 5H), 1.75 – 1.87 (m, 5H), 2.54 (m, 1H), 2.66 (t, 2H), 3.62 (t, 2H), 4.98 (s, 2H), 7.10 – 7.16 (m, 4H), 7.26 (d, 2H), 7.39 (d, 2H), 7.43 (d, 2H), 7.75 (d, 2H).

20

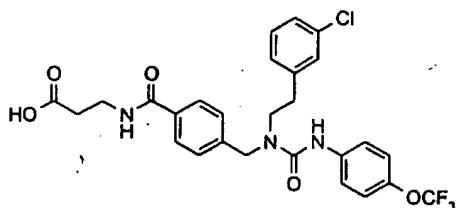
MS (APCI, pos): 584.2, 585.2, 586.2.

The following examples 180 to 229 were all found to displace more than 50% of the glucagon tracer when screened at 1  $\mu\text{M}$  concentration in the glucagon binding assay II. The compounds are all expected to be present in the library.

25

EXAMPLE 180 (general procedure (J))

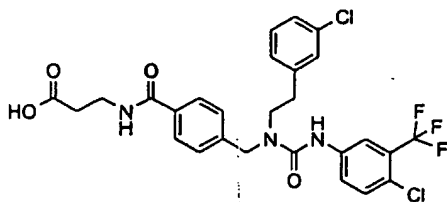
3-{4-[1-[2-(3-Chlorophenyl)ethyl]-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



5

EXAMPLE 181 (general procedure (J))

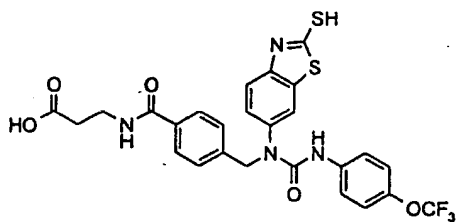
3-{4-[1-[2-(3-Chlorophenyl)ethyl]-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]benzoylamino}propionic acid



10

EXAMPLE 182 (general procedure (J))

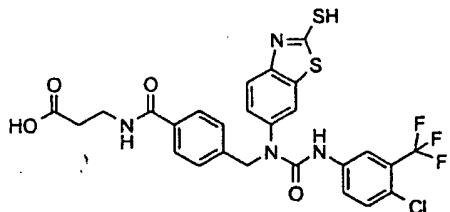
3-{4-[1-[2-(Mercaptobenzothiazol-6-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



15

**EXAMPLE 183 (general procedure (J))**

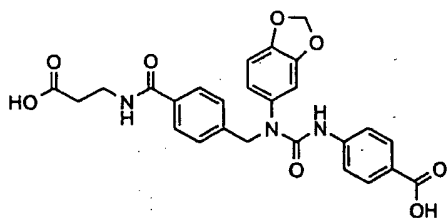
3-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(2-mercaptobenzothiazol-6-yl)ureidomethyl]-benzoylamino}propionic acid



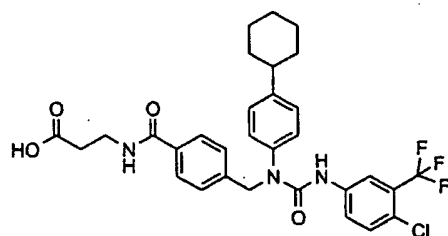
5

**EXAMPLE 184 (general procedure (J))**

4-{3-(Benzo[1,3]dioxo-5-yl)-3-[4-(2-carboxyethylcarbamoyl)benzyl]ureido}benzoic acid

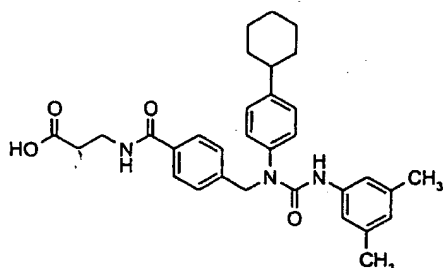
**10 EXAMPLE 185 (general procedure (J))**

3-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}propionic acid



EXAMPLE 186 (general procedure (J))

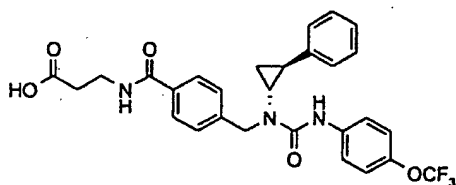
3-{4-[1-(4-Cyclohexylphenyl)-3-(3,5-dimethylphenyl)ureidomethyl]benzoylamino}propionic acid



5

EXAMPLE 187 (general procedure (J))

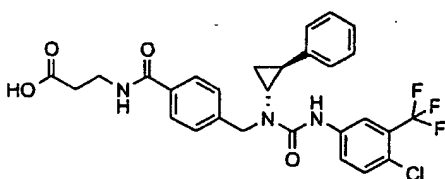
3-{4-[1-(2-Phenylcyclopropyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



10

EXAMPLE 188 (general procedure (J))

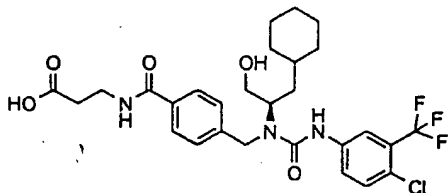
3-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(2-phenylcyclopropyl)ureidomethyl]benzoylamino}propionic acid



15

**EXAMPLE 189 (general procedure (J))**

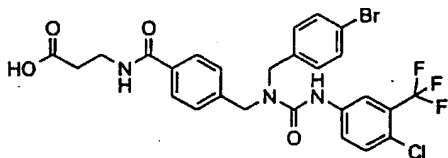
3-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(2-cyclohexyl-1-hydroxymethylethyl)ureido-methyl]benzoylamino}propionic acid



5

**EXAMPLE 190 (general procedure (J))**

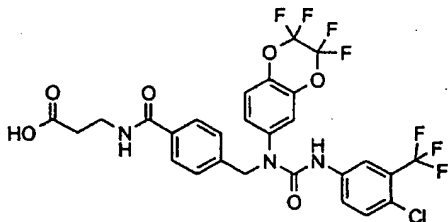
3-{4-[1-(4-Bromobenzyl)-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]benzoylamino}-propionic acid



10

**EXAMPLE 191 (general procedure (J))**

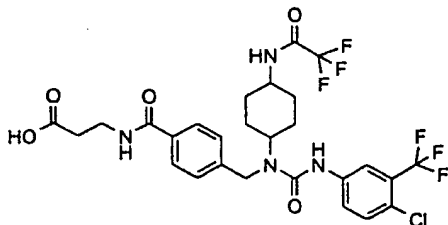
3-{4-[3-(4-Chloro-3-trifluoromethyl-phenyl)-1-(2,2,3,3-tetrafluoro-2,3-dihydro-benzo[1,4]-dioxin-6-yl)ureidomethyl]benzoylamino}propionic acid



15

**EXAMPLE 192 (general procedure (J))**

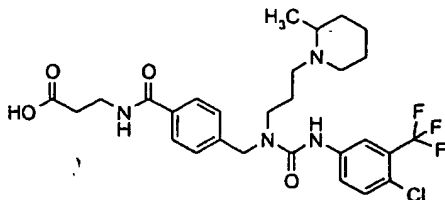
3-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-[4-(2,2,2-trifluoroacetylaminocyclohexyl)ureido-methyl]benzoylamino}propionic acid



20

EXAMPLE 193 (general procedure (J))

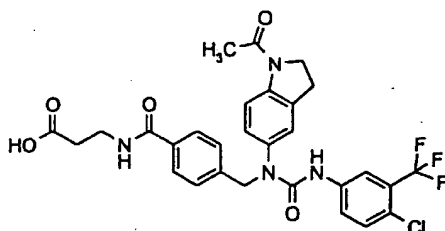
3-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-[3-(2-methylpiperidin-1-yl)propyl]ureidomethyl]-benzoylamino}propionic acid



5

EXAMPLE 194 (general procedure (J))

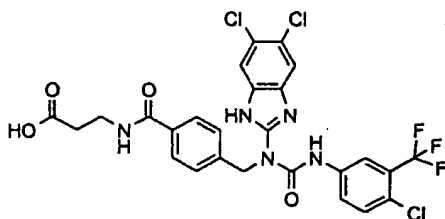
3-{4-[1-(1-Acetyl-2,3-dihydro-1H-indol-5-yl)-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]-benzoylamino}propionic acid



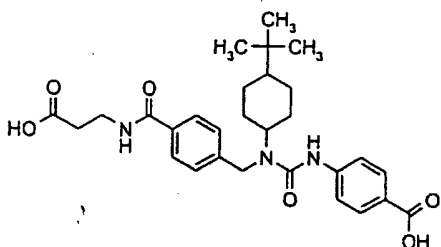
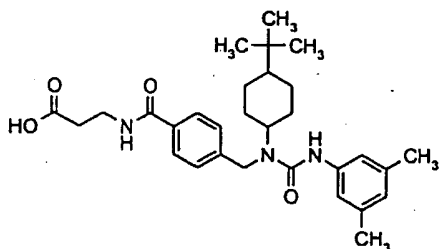
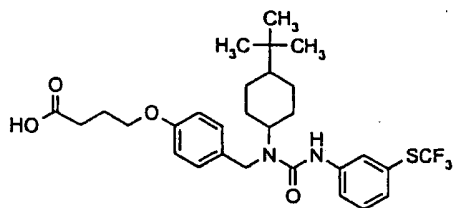
10

EXAMPLE 195 (general procedure (J))

3-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(5,6-dichloro-1H-benzimidazol-2-yl)ureidomethyl]-benzoylamino}propionic acid



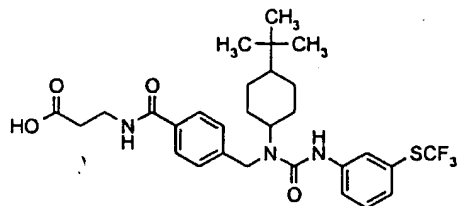
15

EXAMPLE 196 (general procedure (J))4-{3-(4-*tert*-Butylcyclohexyl)-3-[4-(2-carboxyethylcarbamoyl)benzyl]ureido}benzoic acid5 EXAMPLE 197 (general procedure (J))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dimethylphenyl)ureidomethyl]benzoylamino}propionic acid10 EXAMPLE 198 (general procedure (J))4-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-trifluoromethylsulfonylphenyl)ureidomethyl]phenoxy}-butyric acid



EXAMPLE 199 (general procedure (J))

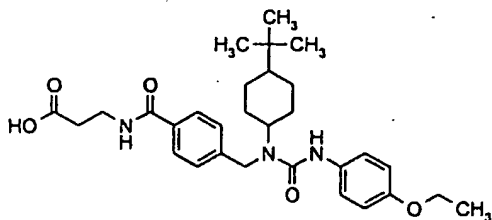
3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-trifluoromethylsulfanylphenyl)ureidomethyl]benzoyl-  
amino}propionic acid



5

EXAMPLE 200 (general procedure (J))

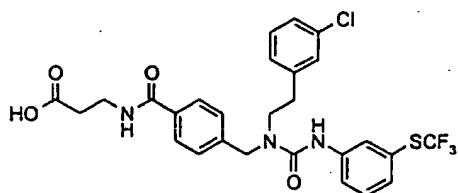
3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-ethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



10

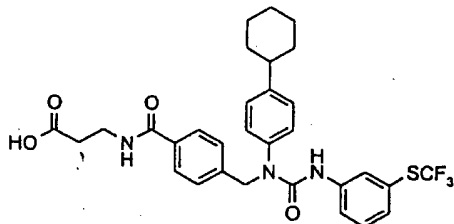
EXAMPLE 201 (general procedure (J))

3-{4-[1-[2-(3-Chlorophenyl)ethyl]-3-(3-trifluoromethylsulfanylphenyl)ureidomethyl]benzoyl-  
amino}propionic acid



EXAMPLE 202 (general procedure (J))

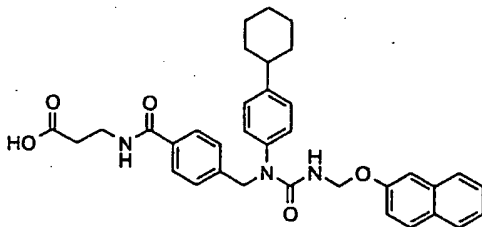
3-{4-[1-(4-Cyclohexylphenyl)-3-(3-trifluoromethylsulfanylphenyl)ureidomethyl]benzoylamino}-propionic acid



5

EXAMPLE 203 (general procedure (J))

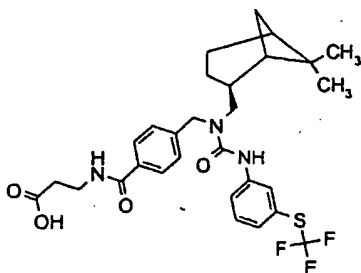
3-{4-[1-(4-Cyclohexylphenyl)-3-(naphthalen-2-yloxymethyl)ureidomethyl]benzoylamino}-propionic acid



10

EXAMPLE 204 (general procedure (J))

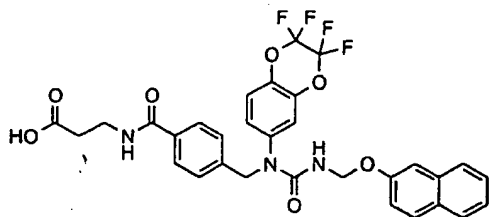
3-{4-[1-(6,6-Dimethylbicyclo[3.1.1]hept-2-ylmethyl)-3-(3-trifluoromethylsulfanylphenyl)ureidomethyl]benzoylamino}propionic acid



15

EXAMPLE 205 (general procedure (J))

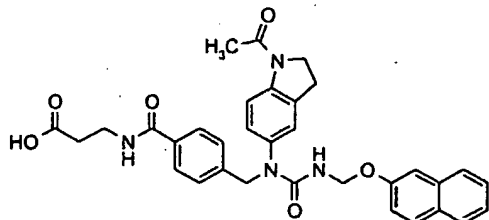
3-{4-[3-(Naphthalen-2-yloxymethyl)-1-(2,2,3,3-tetrafluoro-2,3-dihydro-benzo[1,4]dioxin-6-yl)-ureidomethyl]benzoylamino}propionic acid



5

EXAMPLE 206 (general procedure (J))

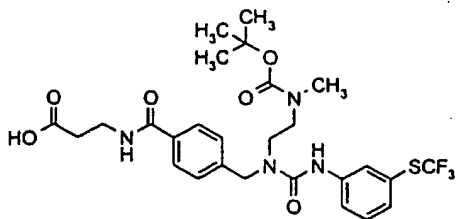
3-{4-[1-(1-Acetyl-2,3-dihydro-1H-indol-5-yl)-3-(naphthalen-2-yloxymethyl)ureidomethyl]benzoylamino}propionic acid



10

EXAMPLE 207 (general procedure (J))

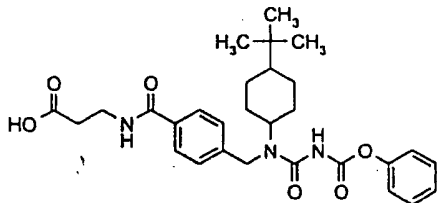
3-{4-[1-[2-(N-tert-Butoxycarbonyl-N-methylamino)ethyl]-3-(3-trifluoromethylsulfanylphenyl)-ureidomethyl]benzoylamino}propionic acid



15

EXAMPLE 208 (general procedure (J))

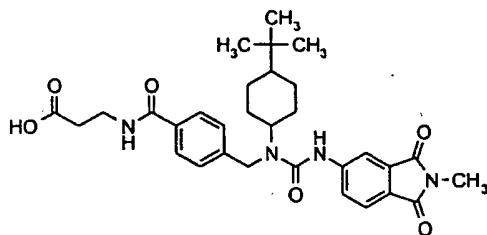
3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(phenoxy carbonyl)ureidomethyl]benzoylamino}propionic acid



5

EXAMPLE 209 (general procedure (J))

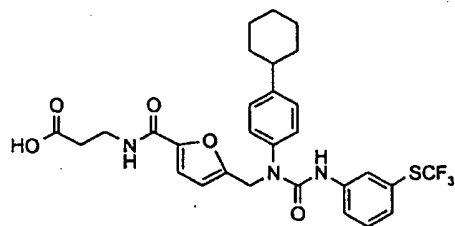
3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(2-methyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-ureidomethyl]benzoylamino}propionic acid



10

EXAMPLE 210 (general procedure (J))

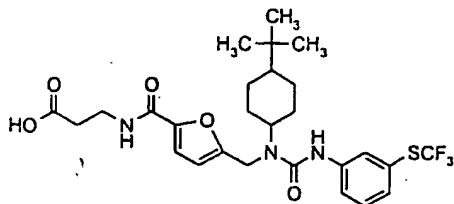
3-({5-[1-(4-cyclohexylphenyl)-3-(3-trifluoromethylsulfanylphenyl)ureidomethyl]furan-2-carbonyl}amino)propionic acid



15

**EXAMPLE 211 (general procedure (J))**

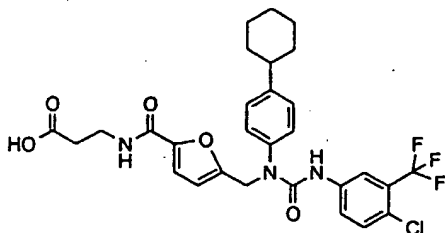
3-((5-[1-(4-*tert*-Butylcyclohexyl)-3-(3-trifluoromethylsulfonylphenyl)ureidomethyl]furan-2-carbonyl)amino)propionic acid



5

**EXAMPLE 212 (general procedure (J))**

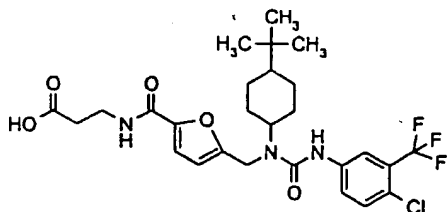
3-((5-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]furan-2-carbonyl)amino)propionic acid



10

**EXAMPLE 213 (general procedure (J))**

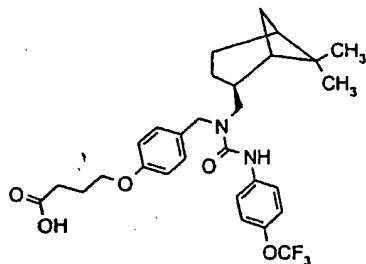
3-((5-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]furan-2-carbonyl)amino)propionic acid



15

**EXAMPLE 214 (general procedure (J))**

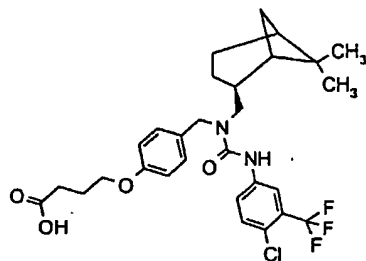
4-{4-[1-(6,6-Dimethylbicyclo[3.1.1]hept-2-ylmethyl)-3-(4-trifluoromethoxyphenyl)ureido-methyl]phenoxy}butyric acid



5

**EXAMPLE 215 (general procedure (J))**

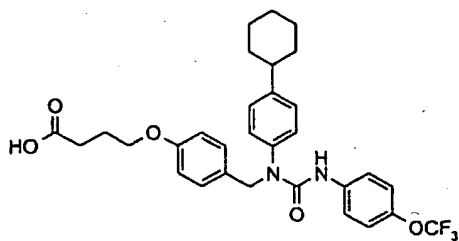
4-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(6,6-dimethylbicyclo[3.1.1]hept-2-ylmethyl)-ureidomethyl]phenoxy}butyric acid



10

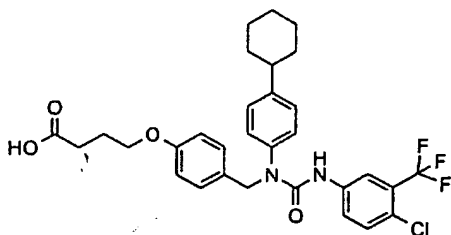
**EXAMPLE 216 (general procedure (J))**

4-{4-[1-(4-Cyclohexylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]phenoxy}butyric acid



EXAMPLE 217 (general procedure (J))

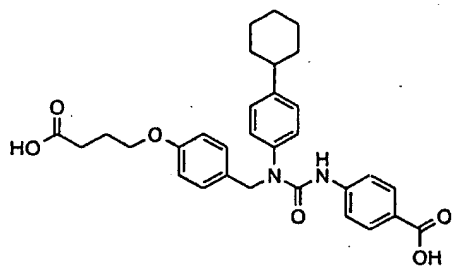
4-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]phenoxy}-butyric acid



5

EXAMPLE 218 (general procedure (J))

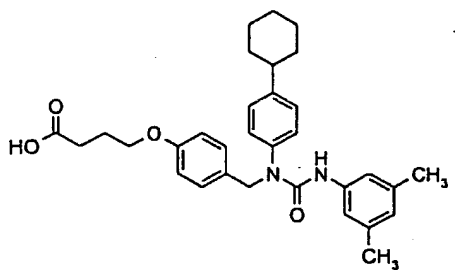
4-[3-[4-(3-Carboxypropoxy)benzyl]-3-(4-cyclohexylphenyl)ureido]benzoic acid

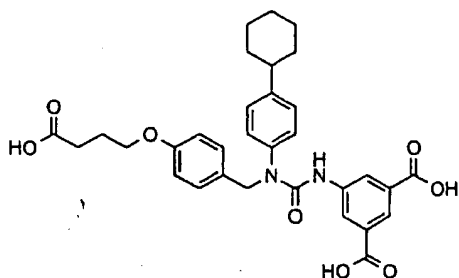
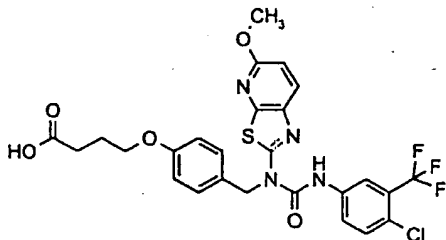
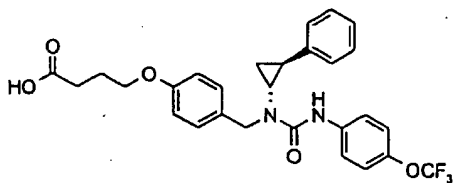
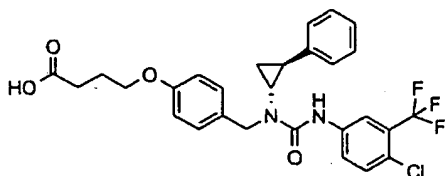


10

EXAMPLE 219 (general procedure (J))

4-{4-[1-(4-Cyclohexylphenyl)-3-(3,5-dimethylphenyl)ureidomethyl]phenoxy}butyric acid

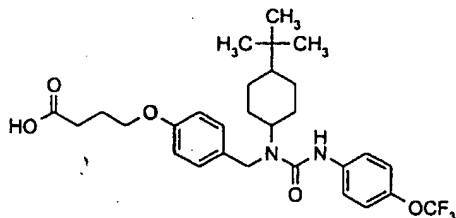


EXAMPLE 220 (general procedure (J))5-[3-[4-(3-Carboxypropoxy)benzyl]-3-(4-cyclohexylphenyl)ureido]isophthalic acid5 EXAMPLE 221 (general procedure (J))4-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(5-methoxythiazolo[5,4-b]pyridin-2-yl)ureido-methyl]phenoxy}butyric acid10 EXAMPLE 222 (general procedure (J))4-{4-[1-(2-Phenylcyclopropyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]phenoxy}butyric acidEXAMPLE 223 (general procedure (J))15 4-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(2-phenylcyclopropyl)ureidomethyl]phenoxy}-butyric acid



EXAMPLE 224 (general procedure (J))

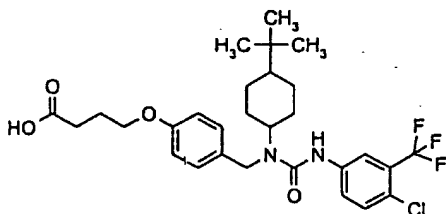
4-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]phenoxy}butyric acid



5

EXAMPLE 225 (general procedure (J))

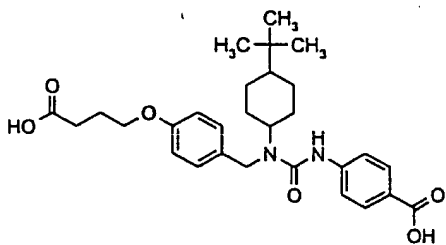
4-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]phenoxy}-butyric acid



10

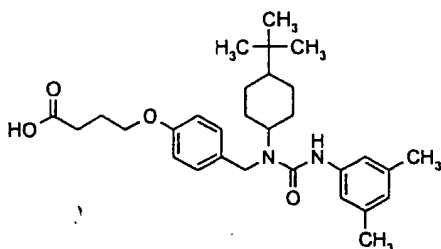
EXAMPLE 226 (general procedure (J))

4-{3-(4-*tert*-Butylcyclohexyl)-3-[4-(3-carboxypropoxy)benzyl]ureido}benzoic acid



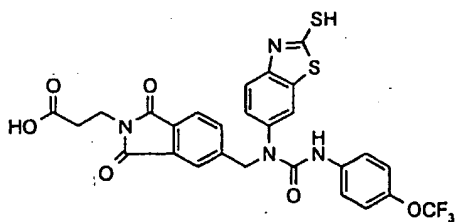
**EXAMPLE 227 (general procedure (J))**

4-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dimethylphenyl)ureidomethyl]phenoxy}butyric acid



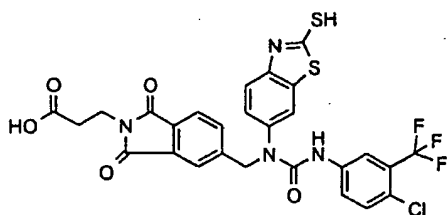
5 **EXAMPLE 228 (general procedure (J))**

3-{5-[1-(2-Mercaptobenzothiazol-6-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-1,3-dioxo-1,3-dihydro-isoindol-2-yl}propionic acid



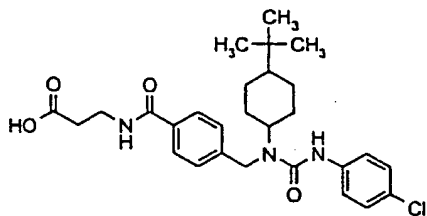
10 **EXAMPLE 229 (general procedure (J))**

3-{5-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(2-mercaptobenzothiazol-6-yl)ureidomethyl]1,3-dioxo-1,3-dihydro-isoindol-2-yl}propionic acid



15 **EXAMPLE 230 (General procedure (J))**

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]benzoylamino}propionic acid

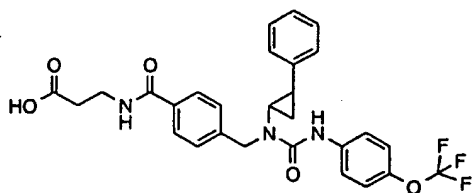


<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.80 (s, 9H), 0.94 (m, 1H), 1.11 (qt, 2H), 1.39 (qt, 2H), 1.69 (m, 4H), 2.45 (t, 2H), 3.44 (qt, 2H), 4.05 (m, 1H), 4.59 (s, 2H), 7.27 (d, 2H), 7.31 (d, 2H), 7.48 (d, 2H), 7.45 (d, 2H), 8.44 (t, 1H), 8.47 (s, 1H), 12.30 (brd s, 1H).

5 MS (APCI, pos): 516.2, 514.2, 361.2, 362.2, 289.2.

EXAMPLE 231 (general procedure (J))

3-[4-[1-(2-Phenylcyclopropyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino]-propionic acid



10

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.36 – 1.50 (m, 2H), 2.36 (m, 1H), 2.45 (t, 2H), 2.79 (quintet, 1H), 3.43 (qt, 2H), 4.54 (d, 1H), 4.75 (d, 1H), 7.06 (d, 2H), 7.16 (t, 1H), 7.23 – 7.30 (m, 6H), 7.58 (d, 2H), 7.74 (d, 2H), 8.46 (s, 1H), 8.48 (t, 1H), 12.20 (brd s, 1H).

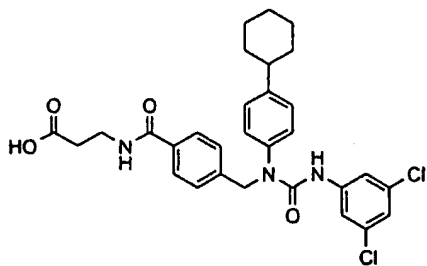
15

MS (APCI, pos): 542.2, 543.2, 544.2, 339.1.

EXAMPLE 232 (general procedure (J))

3-[4-[1-(4-Cyclohexylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino]propionic acid

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25

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.10 – 1.42 (m, 5H), 1.60 – 1.80 (m, 5H), 2.45 (t, 2H), 3.43 (qt, 2H), 4.92 (s, 2H), 7.12 – 7.20 (M, 5H), 7.30 (d, 2H), 7.58 (s, 2H), 7.74 (d, 2H), 8.46 (t, 1H), 8.55 (s, 1H).

MS (APCI, pos): 568.2, 569.2, 570.2, 571.2.

Alternative method for the preparation of the compound:

To a solution of 4-formylbenzoic acid (27.4 g, 0.18 mol) in DMF (300 mL) was added *N*-ethyl-*N*'-3-dimethylaminopropylcarbodiimide (34.5 g, 0.18 mol) and *N*-hydroxybenzotriazole (29.9 g, 0.22 mol). The resulting mixture was stirred at room temperature for 1 hour, then  $\beta$ -alanine ethyl ester hydrochloride (65.4 g, 0.42 mol) and diisopropylethylamine (76 mL, 0.44 mol) was added. After 16 hours stirring at ambient temperature the reaction mixture was partitioned between water (600 mL) and ethyl acetate (600 mL). The organic phase was washed successively with hydrochloric acid (1N, 300 mL), saturated aqueous ammonium chloride (300 mL), water (2 x 300 mL) and brine (300 mL). The solvent was removed by rotary evaporation to leave an oil, which crystallised upon standing to afford 29.0 g (65%) of 3-(4-formylbenzoylamino)propionic acid ethyl ester.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.18 (t, 3H); 2.62 (t, 2H); 3.54 (q, 2H); 4.09 (q, 2H); 8.00 (s, 4H); 8.78 (t, 1H); 10.08 (s, 1H).

To a well stirred solution of 3-(4-formylbenzoylamino)propionic acid ethyl ester (13.8 g, 55.3 mmol) in ethanol (150 mL) was added a solution of 4-cyclohexylaniline (9.70 g, 55.3 mmol) in ethanol (75 mL). The mixture was heated to reflux for 30 minutes, and then acetic acid (50 mL) and sodium cyanoborohydride (3.50 g, 55.5 mmol) were added. After 10 minutes of additional heating, the mixture was cooled on an ice-bath. The solid precipitate was collected by filtration, washed several times with cold water and dried in a vacuum oven overnight to afford 18.16 g (80%) of 3-{4-[(4-cyclohexylphenylamino)methyl]benzoylamino}propionic acid ethyl ester.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.28 (t, 3H); 1.35 (m, 5H); 1.78 (m, 5H); 2.38 (m, 1H); 2.64 (t, 2H); 3.74 (q, 2H); 4.18 (q, 2H); 4.36 (s, 2H); 6.53 (d, 2H); 6.81 (bt, 1H); 7.00 (d, 2H); 7.43 (d, 2H); 7.72 (d, 2H).

3-{4-[(4-Cyclohexylphenylamino)methyl]benzoylamino}propionic acid ethyl ester (15.0 g, 0.37 mol) was dissolved in dichloromethane (250 mL), and 3,5-dichlorophenylisocyanate (6.9 g, 0.37 mol) was added. The mixture was stirred overnight at room temperature. The solvent was removed by rotary evaporation, and the crystalline residue was re-dissolved in ethanol (400 mL). Sodium hydroxide (100 mL, 4N) was added, and the reaction mixture was left at

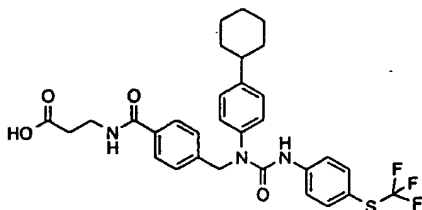
room temperature for 30 min. Water (600 mL) was added and the mixture was cooled on an ice bath. The clear solution was then acidified with hydrochloric acid (100 mL, 4N), and the resulting precipitate subsequently collected by filtration. Recrystallisation from acetonitrile / water afforded 15.5 g of the title compound as a white powder.

5

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.36 (m, 5H); 1.78 (m, 6H); 2.50 (t, 2H); 3.44 (q, 2H); 4.92 (s, 2H); 7.12 (d, 1H); 7.16 (d, 2H); 7.21 (d, 2H); 7.32 (d, 2H); 7.60 (d, 2H); 7.75 (d, 2H); 8.45 (t, 1H); 8.53 (s, 1H); 12.20 (bs, 1H).

10 EXAMPLE 233 (general procedure (J))

3-{4-[1-(4-Cyclohexylphenyl)-3-(4-trifluoromethylsulfanylphenyl)-ureidomethyl]benzoylamino}-propionic acid



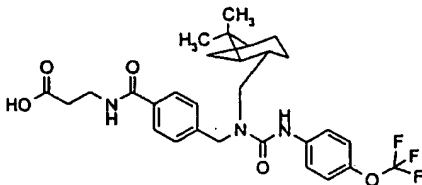
15  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.10 – 1.35 (m, 5H), 1.50 – 1.75 (m, 5H), 2.40 (m, 1H), 2.47 (t, 2H), 3.45 (t, 2H), 4.81 (s, 2H), 6.98 (d, 2H), 7.10 (d, 2H), 7.21 (d, 2H), 7.33 (d, 2H), 7.36 (d, 2H), 7.57 (d, 2H).

MS (APCI, pos): 600.2, 601.2, 602.2.

20

EXAMPLE 234 (general procedure (J))

3-{4-[1-(((1S,2R,5R)-6,6-Dimethylbicyclo[3.1.1]hept-2-yl)methyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



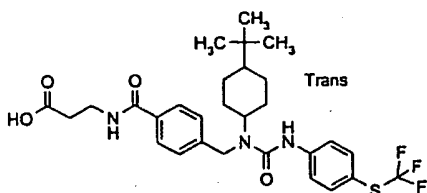
25

$^1\text{H}$  NMR ( $\text{MeOH}-d_4$ ):  $\delta$  0.90 (d, 1H), 1.05 (s, 3H), 1.15 (s, 3H), 1.49 (m, 1H), 1.80 - 1.95 (m, 5H), 2.36 - 2.47 (m, 2H), 2.62 (t, 2H), 3.40 (d, 2H), 3.61 (t, 2H), 4.70 (qt, 2H), 7.16 (d, 2H), 7.35 (d, 2H), 7.41 (d, 2H), 7.78 (d, 2H).

5 MS (APCI, pos): 562.2, 563.1.

EXAMPLE 235 (general procedure (J))

3-(4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-(trifluoromethoxysulfonylphenyl)ureidomethyl]-benzoylamino}propionic acid



10

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  0.80 (s, 9H), 0.90 (d, 1H), 1.20 (qt, 2H), 1.40 (qt, 2H), 1.90 (t, 4H), 2.75 (t, 2H), 3.70 (qt, 2H), 4.10 (brd t, 1H), 4.50 (s, 2H), 6.50 (s, 1H), 6.90 (t, 1H), 7.20 (d, 2H), 7.40 (d, 2H), 7.50 (d, 2H), 7.70 (d, 2H).

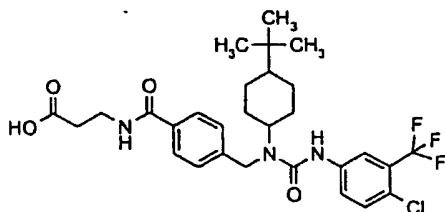
15

MS (APCI, pos): 580.2, 581.2.

EXAMPLE 236 (general procedure (J))

3-(4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]benzoyl-amino}propionic acid

20

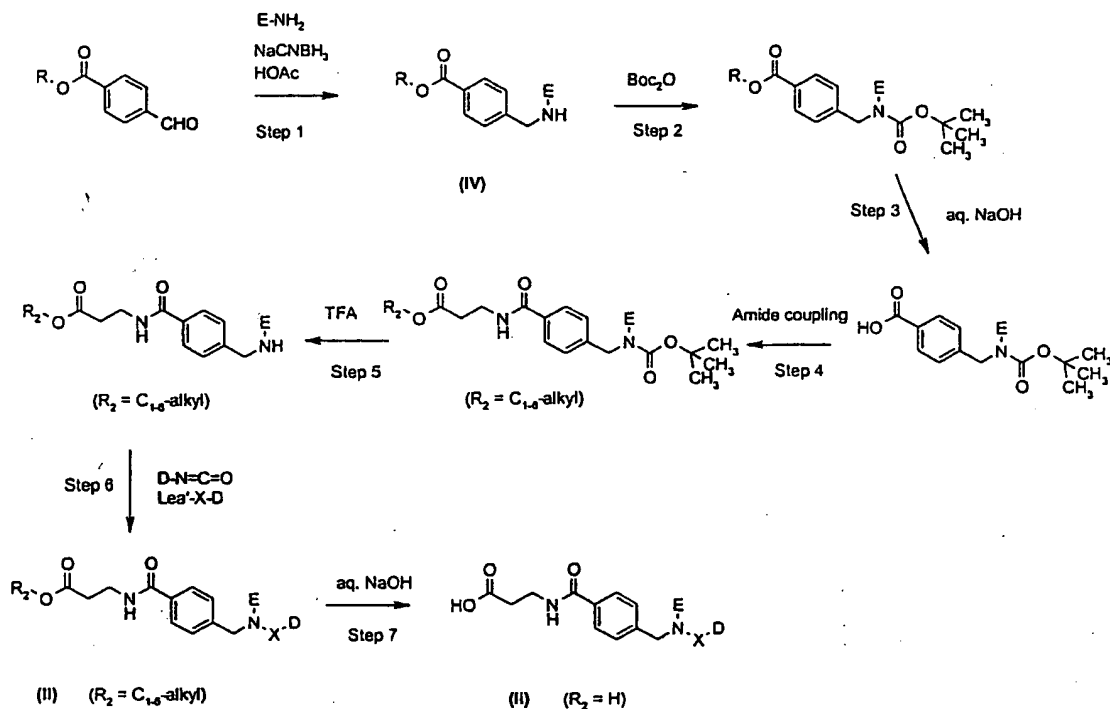


25

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  0.78 (s, 9H), 1.10 (m, 1H), 1.33 (m, 2H), 1.50 (m, 4H), 1.75 (m, 2H), 2.40 (t, 2H), 3.43 (qt, 2H), 4.24 (quintet, 1H), 4.69 (s, 2H), 7.27 (d, 2H), 7.53 (d, 1H), 7.74 - 7.79 (m, 3H), 8.03 (s, 1H), 8.45 (t, 1H), 8.85 (s, 1H); 12.00 (brd s, 1H).

MS (APCI, pos): 582.2, 361.2.

General procedure (K) for the solution phase synthesis of compounds of the general formula (II):



5

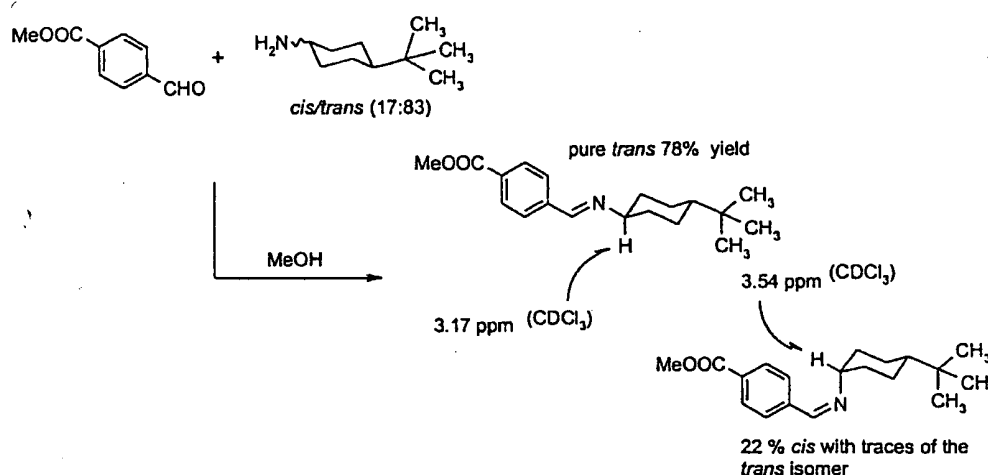
wherein  $R$  is  $C_{1-6}$ -alkyl,

$V$ ,  $X$ ,  $D$ , and  $E$  are as defined in general formula (I), and

10  $Lea'$  is a leaving group such as  $-OSu$ , chloro, phenoxy, or 4-nitrophenoxy.

In case the intermediate of the formula (IV) is a mixture of isomers, separation of these can either be performed by column chromatography of the intermediate of the formula (IV) or crystallisation of the intermediate imine.

15

Step 1: *trans*-4-[(4-*tert*-Butylcyclohexylamino)methyl]benzoic acid methyl ester

- 5 4-Formylbenzoic acid methyl ester (10.6 g, 64.4 mmol) was dissolved in methanol (200 mL). A 17:83 *cis/trans* mixture of 4-*tert*-butylcyclohexylamine (10.0 g, 64.4 mmol, Aldrich) was added, leading to immediate precipitation of white crystals. The mixture was heated to reflux for 30 min to complete imine formation, then cooled to 0°C on an ice bath. The crystalline pure *trans*-4-[(4-*tert*-butylcyclohexylimino)methyl]benzoic acid methyl ester was then collected by filtration, and dried overnight in vacuo. Yield: 15.3 g (78%).

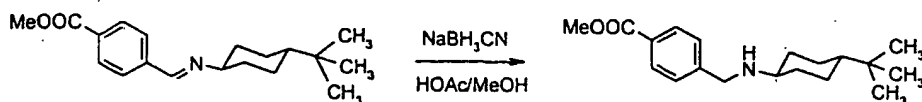
<sup>1</sup>H NMR (CDCl<sub>3</sub>), 300 MHz: δ 8.37 ppm. (s, 1H); 8.06 (d, 2H); 7.77 (d, 2H); 3.92 (s, 3H); 3.17 (m, 1H); 1.83 (m, 4H); 1.60 (m, 2H), 1.09 (m, 3H); 0.87 (s, 9H).

- 15 Micro Analysis: Calculated for C<sub>19</sub>H<sub>27</sub>NO<sub>2</sub>  
C: 75.71%, H: 9.03%, N: 4.65%. Found:  
C: 75.60%, H: 9.37%, N: 4.68%.

- The mother liquid was taken to dryness to leave 4.2 g (22%) white solid, which according to NMR consisted mainly of the imino *cis* isomer.

<sup>1</sup>H NMR (CDCl<sub>3</sub>), 300 MHz: δ 8.36 ppm. (s, 1H); 8.07 (d, 2H); 7.81 (d, 2H); 3.92 (s, 3H); 3.54 (m, 1H); 1.55 - 1.92 (m, 8H); 1.14 (m, 1H); 0.90 (s, 9H).





*trans*-4-[(4-*tert*-Butylcyclohexylimino)methyl]benzoic acid methyl ester (21.0 g, 69.2 mmol) was suspended in methanol (300 mL), and acetic acid (50 mL) was added. To the resulting clear solution was added sodium cyanoborohydride (3.5 g, 55.5 mmol), and the mixture was stirred at ambient temperature for 30 min. The reaction volume was then reduced to one third by rotary evaporation, and ethyl acetate (500 mL) was added. The organic phase was washed with sodium carbonate solution (5%, 500 mL), and dried with Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed by rotary evaporation to leave the title material as a white crystalline solid sufficiently pure for further reactions. Yield: 21.1 g (100%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>), 300 MHz: δ 7.98 ppm. (d, 2H); 7.38 (d, 2H); 3.90 (s, 3H); 3.86 (s, 2H); 2.39 (m, 1H); 2.01 (m, 2H); 1.77 (m, 2H); 1.51 (bs, 1H); 0.93-1.18 (m, 5H); 0.82 (s, 9H).

HPLC-MS (Method B: R<sub>t</sub> = 4.87 m/z = 304 (M + 1).

Alternatively, step 1 can be performed in the same way as step A of the general procedure (F).

**Step 2: *trans*-4-[(*N*-(*tert*-Butoxycarbonyl)-*N*-(4-*tert*-butylcyclohexyl)amino)methyl]benzoic acid methyl ester**

*trans*-4-[(4-*tert*-Butylcyclohexylamino)methyl]benzoic acid methyl ester (20.0 g, 65.9 mmol) was dissolved in THF (300 mL). Di-*tert*-butylpyrocarbonate (16.0 g, 73.4 mmol) and diisopropylethylamine (12.0 g, 92.9 mmol) was added and the clear solution stirred overnight at ambient temperature. Solvent was removed by rotary evaporation.

**Step 3: *trans*-4-[(*N*-(*tert*-Butoxycarbonyl)-*N*-(4-*tert*-butylcyclohexyl)amino)methyl]benzoic acid**

The crystalline residue from step 2 was re-dissolved in ethanol (200 mL) and aqueous sodium hydroxide solution (100 mL, 4N) was added whereafter the mixture was heated to 70°C for 4 hours. After cooling, the reaction volume was reduced to one third by rotary evaporation, and water (300 mL) was added. The mixture was extracted with diethyl ether (2 x 200 mL) to remove traces of non-hydrolysed material. The aqueous phase was then acidified to pH 3.0 by addition of aqueous 4N HCl, whereupon the title material separated out of solution

as compact crystals. The crystals were washed once with water and dried overnight in a vacuum oven (40°C). Yield: 24.3 g (93%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>), 300 MHz: δ 8.04 ppm. (d, 2H); 7.31 (d, 2H); 4.39 (bs, 2H); 4.05 (bs, 1H);  
5 1.78 (bd, 4H); 0.95-1.65 (m, 14 H); 0.83 (s, 9H). The signals were broad due to the presence  
of *cis/trans* carbamate isomers.

Micro analysis Calculated for C<sub>23</sub>H<sub>35</sub>NO<sub>4</sub>:

C, 70.92%; H, 9.06%; N, 3.60%. Found:

10 C, 70.67%; H, 9.36%; N: 3.57%.

Step 4: Methyl *trans*-4-[[*N*-(*tert*-butoxycarbonyl)-*N*-(4-*tert*-butylcyclohexyl)amino]methyl]-benzoylaminopropanoate

*Trans*-4-[[*N*-(*tert*-butoxycarbonyl)-*N*-(4-*tert*-butylcyclohexyl)amino]methyl]benzoic acid (22.0  
15 g, 56.5 mmol) and 1-hydroxybenzotriazole (8.6 g, 57.0 mmol, containing 12% w/w water)  
was dissolved in DMF (300 mL). *N*-Dimethylaminopropyl-*N*'-ethylcarbodiimide hydrochloride  
(10.9 g, 56.8 mmol), β-alanine methyl ester (8.4 g, 60 mmol) and diisopropylethylamine (25  
mL, 142 mmol) were added and the clear solution stirred at 20°C for 16 hours. Solvent was  
removed by rotary evaporation and the residual oil re-dissolved in ethyl acetate (500 mL).  
20 The organic phase was washed with 5% aqueous sodium hydrogen carbonate solution (2 x  
500 mL), 0.5 M citric acid (2 x 250 mL) and brine before being dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>.  
Solvent was removed and the residual oil evaporated twice from acetonitrile. The oil was  
used without further purification. Yield: 24.0 g (89%).

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>), 300 MHz: δ 7.69 (d, 2H); 7.28 (d, 2H); 6.81 (t, 1H); 4.38 (bs, 2H); 3.23 (s,  
3H); 3.21 (t, 2H); 2.66 (t, 2H); 1.75 (bd, 4H); 0.95-1.65 (m, 14 H); 0.80 (s, 9H).

Step 5: Methyl *trans*-4-[[*N*-(4-*tert*-butylcyclohexyl)aminomethyl]benzoylaminopropanoate tri-fluoroacetate

30 Methyl *trans*-4-[[*N*-(*tert*-butoxycarbonyl)-*N*-(4-*tert*-butylcyclohexyl)amino]methyl]benzoyl-  
aminopropanoate (19.5 g, 41.1 mmol) was dissolved in a mixture of TFA (200 mL) and di-  
chloromethane (200 mL), while cooling on an ice bath. The ice bath was removed and the  
mixture allowed to stir at room temperature for 30 min. Solvent was removed by rotary  
evaporation, and the crystalline residue recrystallized from ethyl acetate/heptane. Yield: 14.8  
35 g (74%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>), 300 MHz: δ 9.98 (trace of TFA); 8.06 (bs, 2H); 7.73 (d, 2H); 7.41 (d, 2H); 7.34 (t, 1H); 4.21 (t, 2H); 3.75 (s, 3H); 3.74 (t, 2H); 3.04 (m, 1H); 2.70 (t, 2H); 2.17 (bd, 2H); 1.95 (bd, 2H); 1.50 (m, 2H); 0.92-1.15 (m, 3H); 0.85 (s, 9H).

5

Micro analysis. Calculated for C<sub>22</sub>H<sub>34</sub>N<sub>2</sub>O<sub>3</sub>·C<sub>2</sub>HF<sub>3</sub>O<sub>2</sub>:

C, 59.00%; H, 7.22%; N, 5.73%. Found:

C, 58.95%; H, 7.37%; N: 5.70%.

10 General procedure for forming isocyanates from (substituted) anilines and diphosgene to be used in step 6:

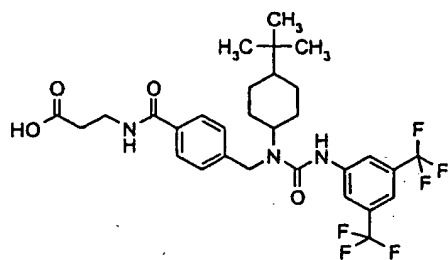
To a solution of the amine in anhydrous toluene was added 1N HCl in diethyl ether (5 eq). A precipitate formed. The toluene was evaporated. To the solid was added more anhydrous toluene and the toluene was evaporated again to remove excess HCl. This procedure was repeated 2-3 times. To a mixture of the solid in toluene (about 10 g in 300 mL) was added diphosgene (trichloromethyl chloroformate) (10 eq or more) or phosgene. The mixture was refluxed under nitrogen overnight. A clear solution was obtained. If more solid was present, more diphosgene was added and reflux continued. When a clear solution was obtained, the reaction was concentrated in vacuo at 60-90°C to remove the toluene and excess diphos-  
gene until the theoretical weight was obtained. To the crude isocyanate was added more anhydrous toluene and concentrated again to remove excess HCl. The crude isocyanate was used without further purification.

25

This method gives the isocyanates in pure form, which may be used in step 6.

EXAMPLE 237 (general procedure (K))

3-(4-[3-(3,5-Bis-trifluoromethylphenyl)-1-(trans-4-tert-butylcyclohexyl)ureidomethyl]benzoyl-amino)propionic acid



30

Step 6, using a phenyl carbamate or nitrophenyl carbamate

3,5-Bis-(trifluoromethyl)aniline (2.0 g, 8.7 mmol) was dissolved in dichloromethane (80 mL) and *N,N*-diisopropylethylamine (1.6 mL, 9.6 mmol) was added followed by slow addition of phenyl chloroformate (1.1 mL, 8.7 mmol). The resulting mixture was stirred at room temperature for 16 hours. The mixture was successively washed with 1N hydrochloric acid (3 x 100 mL), water (3 x 100 mL), a mixture of water and saturated aqueous sodium hydrogen carbonate (1:1, 2 x 100 mL) and a mixture of water and saturated aqueous sodium chloride (1:1, 3 x 100 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was crystallised from heptane containing a little diethyl ether to afford 1.3 g (43%) of (3,5-bis-trifluoromethyl-phenyl)carbamic acid phenyl ester as a solid.

Calculated for C<sub>15</sub>H<sub>9</sub>F<sub>6</sub>NO<sub>2</sub>:

C, 51.59%; H, 2.60%; N, 4.01%. Found:

C, 51.27%; H, 2.56%; N, 4.01%;

C, 51.40%; H, 2.57%; N, 3.92%.

The above carbamic acid phenyl ester (1.0 g, 2.9 mmol) was mixed with 3-{4-[(4-*tert*-butyl-cyclohexylamino)methyl]benzoylamino}propionic acid methyl ester, trifluoroacetate (1.07 g, 2.9 mmol), prepared as described above and triethylamine (1.2 mL, 8.6 mmol) in dichloromethane (55 mL) and the resulting mixture was refluxed for 4 hours. The cooled reaction mixture was diluted with toluene (50 mL) and washed with water (3 x 50 mL) and a mixture of water and saturated aqueous sodium chloride (1:1, 3 x 100 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo to afford 1.2 g (67%) of 3-{4-[3-(3,5-bis-trifluoromethylphenyl)-1-(4-*tert*-butyl-cyclohexyl)ureidomethyl]benzoylamino}propionic acid methyl ester as a solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.83 (9H, s), 0.9-1.5 (5H, m), 1.88 (4H, bt), 7.62 (H, t), 3.72 (5H, m), 4.18 (1H, bt), 4.57 (2H, s), 6.80 (1H, s), 6.90 (1H, t), 7.38 (2H, d), 7.46 (1H, s), 7.77 (2H, d), 7.80 (2H, s).

HPLC-MS (Method B): R<sub>t</sub> = 9.07 min, m/z = 630 (M + 1).

Step 7:

The above propionic acid methyl ester (1.0 g, 1.6 mmol) was dissolved in warm ethanol (50 mL), and after cooling to room temperature 4N aqueous sodium hydroxide (6 mL) was added. The reaction mixture was stirred at room temperature for 1 hour. Glacial acetic acid

(10 mL) was added and the mixture was concentrated in vacuo. The residue was partitioned between water (50 mL) and ethyl acetate (2 x 50 mL). The combined organic phases were dried (MgSO<sub>4</sub>) and concentrated in vacuo to afford 0.88 g (93%) of the title compound as a solid.

5

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.83 (9H, s), 0.9-1.5 (5H, m), 1.70 (4H, bt), 2.50 (2H, t, below DMSO), 3.45 (2H, q, below water), 4.05 (1H, bt), 4.62 (2H, s), 7.32 (2H, d), 7.60 (2H, d), 8.24 (2H, s), 8.45 (1H, t), 9.00 (1H, s), 12 (1H, bs).

10 HPLC-MS (Method B): R<sub>t</sub> = 8.60 min, m/z = 616 (M + 1).

Calculated for C<sub>30</sub>H<sub>35</sub>F<sub>6</sub>N<sub>3</sub>O<sub>4</sub> x 0.25H<sub>2</sub>O:

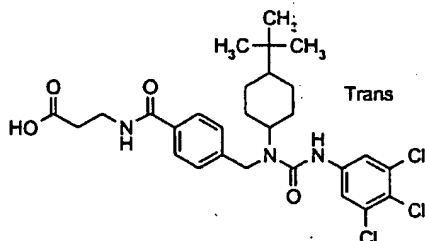
C, 57.47%; H, 5.57%; N, 6.93%. Found:

C, 57.60%; H, 5.81%; N, 6.47%;

15 C, 57.63%; H, 5.76%; N, 6.45%.

EXAMPLE 238 (general procedure (K))

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(3,4,5-trichlorophenyl)ureidomethyl]benzoylamino}-propionic acid



20

Step 6, using isocyanate formed in situ from (substituted) anilines and triphosgene:

Triphosgene (bis-trichloromethylcarbonate) (152 mg, 0.51 mmol) was dissolved in dichloromethane (4 mL) and cooled to 0°C. To this solution a solution of 3,4,5-trichloroaniline (303 mg, 1.54 mmol) and diisopropylethylamine (540 μL, 3.1 mmol) in dichloromethane (3 mL) was added at 0°C over 1 hour. The mixture was then allowed to reach room temperature. To this mixture a solution of methyl *trans*-4-[(4-*tert*-butylcyclohexyl)aminomethyl]benzoylamino-propanoate trifluoroacetate (576 mg, 1.54 mmol) and diisopropylethylamine (800 μL) in dichloromethane (10 mL) was added and stirring at room temperature was continued for 30 minutes. The mixture was diluted with more dichloromethane (10 mL) and washed with satu-

30

rated aqueous citric acid (2 x 20 mL). The organic phase was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo to afford 653 mg (71%) of 3-{4-[1-(4-*trans*-*tert*-butylcyclohexyl)-3-(3,4,5-trichlorophenyl)ureidomethyl]benzoylamino}propionic acid methyl ester as a solid.

- 5  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  0.81 (s, 9H), 0.92 (m, 1H), 1.12 (m, 2H), 1.44 (m, 2H), 1.68 (m, 4H), 2.56 (t, 2H), 3.45 (q, 2H), 3.59 (s, 3H), 4.05 (b t, 1H), 4.58 (s, 2H), 7.30 (d, 2H), 7.78 (d, 2H), 7.83 (s, 2H), 8.44 (t, 1H), 8.75 (s, 1H).

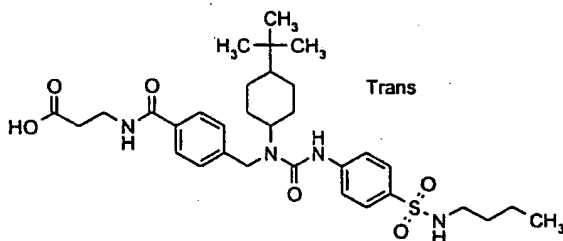
Step 7:

- 10 Hydrolysis of this ester using the method described in example 92, step D afforded the title compound (495 mg, 78%).

- $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  0.82 (s, 9H), 0.91 (m, 1H), 1.10 (m, 2H), 1.39 (m, 2H), 1.71 (m, 4H), 2.51 (t, 2H), 3.35 (q, 2H), 4.01 (t, 1H), 4.59 (s, 2H), 7.30 (d, 2H), 7.78 (d, 2H), 7.85 (s, 2H),  
15 8.46 (t, 1H), 8.76 (s, 1H), 12.21 (b s, 1H).

EXAMPLE 239 (general procedure (K))

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-butylsulfamoylphenyl)ureidomethyl]benzoylamino}-propionic acid



- 25 4-Nitrophenylsulfonyl chloride (3.0 g, 13.5 mmol) was dissolved in THF and a catalytic amount of 4-dimethylaminopyridine and 1-butylamine (4.0 mL, 41 mmol) was added and the mixture was refluxed for 16 hours. The mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (100 mL) and washed with water (50 mL) and a 10% aqueous solution of sodium hydrogen carbonate (50 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to afford 3.01 g (86%) of *N*-butyl-4-nitrobenzenesulfonamide as a solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.89 (3H, t), 1.30 (2H, m), 1.48 (2H, m), 3.03 (2H, t), 4.9 (1H, b), 8.06 (2H, d), 8.37 (2H, d).

Sodium dithionite (11.4 g, 65 mmol) and sodium carbonate (5.6 g, 53 mmol) were dissolved  
5 in water (65 mL) and heated to 70°C. A suspension of the above 4-nitrophenylsulfonamide  
(2.64 g, 10.2 mmol) in methanol (65 mL) was added and the resulting mixture was stirred at  
70°C for 1.5 hour. The cooled mixture was filtered and the volume of the filtrate was reduced  
by 50% in vacuo. The aqueous mixture was extracted with ethyl acetate (3 x 60 mL), and the  
10 combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated in vacuo to afford 0.14 g  
(6%) of 4-amino-*N*-butylbenzenesulfonamide as a solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.80 (3H, t), 1.2-1.4 (4H, m), 2.65 (2H, q), 5.90 (2H, s), 6.60 (2H, d),  
7.04 (1H, t), 7.40 (2H, d).

15 HPLC-MS (Method B): R<sub>t</sub> = 5.15 min, m/z = 229 (M + 1).

The above 4-aminophenylsulfonamide (0.14 g) was dissolved in dichloromethane (6 mL),  
*N,N*-diisopropylethylamine (172 μL, 1 mmol) and phenyl chloroformate (122 μL, 0.92 mmol)  
and the resulting mixture was stirred at room temperature for 16 hours. The reaction mixture  
20 was diluted with dichloromethane (50 mL) and was washed with 1N hydrochloric acid (3 x 20  
mL), water (3 x 20 mL), a mixture of water and a saturated solution of sodium hydrogen car-  
bonate (1:1, 2 x 20 mL) and a mixture of water and a saturated solution of sodium chloride  
(1:1, 2 x 20 mL). Drying (MgSO<sub>4</sub>) and concentration in vacuo afforded crude (4-butyl-  
sulfamoylphenyl)carbamic acid phenyl ester.

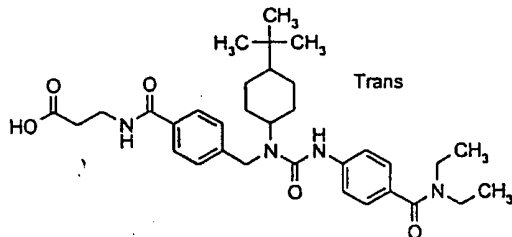
25

From the above crude carbamic acid phenyl ester and 3-{4-[(4-*trans-tert*-butylcyclohexyl-  
amino)methyl]benzoylamino}propionic acid methyl ester trifluoroacetate the title compound  
was obtained similarly as described above.

30 HPLC-MS (Method B): R<sub>t</sub> = 7.37 min, m/z = 615 (M + 1).

**EXAMPLE 240 (general procedure (K))**

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-diethylcarbamoylphenyl)ureidomethyl]benzoylamino}propionic acid



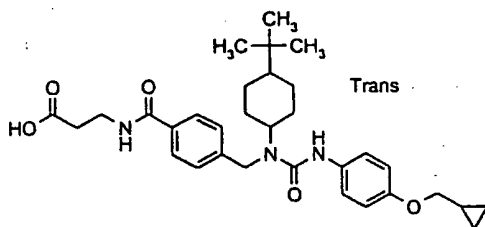
5

The title compound was prepared similarly as described above starting from 4-nitrobenzoyl chloride, diethylamine and 3-{4-[(4-*trans*-*tert*-butylcyclohexylamino)methyl]benzoylamino}-propionic acid methyl ester trifluoroacetate.

10 HPLC-MS (Method B):  $R_t = 6.76$  min,  $m/z = 579$  ( $M + 1$ ).

**EXAMPLE 241 (general procedure (K))**

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-cyclopropylmethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



15

4-Nitrophenol (2.0 g, 14.4 mmol) was dissolved in DMF (50 mL) and potassium carbonate (6.0 g, 43 mmol) and bromomethylcyclopropane (1.51 mL, 16 mmol) were added and the resulting mixture was stirred at room temperature for 16 hours. The mixture was diluted with ethyl acetate (50 mL) and washed with a saturated aqueous solution of sodium chloride (2 x 50 mL). Drying ( $MgSO_4$ ) and concentration afforded 2.23 g (75%) of 1-cyclopropylmethoxy-4-nitrobenzene as an oil.

20  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  0.40 (2H, m), 0.58 (2H, m), 1.30 (1H, m), 3.89 (2H, d), 6.94 (2H, d), 8.12 (2H, d).

25



The above 4-nitrobenzene (2.0 g, 9.5 mmol) was dissolved in ethanol (50 mL) and tin(II) chloride dihydrate (10.7 g, 48 mmol) was added and the mixture was refluxed for 24 hours. After cooling, the mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate (40 mL) and 1N aqueous sodium hydroxide (180 mL). This mixture was filtered through  
5 celite. The aqueous phase was extracted with ethyl acetate (2 x 50 mL) and the combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated in vacuo to afford 0.88 g (52%) of 4-cyclopropylmethoxyaniline.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.25 (2H, m), 0.53 (2H, m), 1.15 (1H, m), 3.63 (2H, d), 4.55 (2H, s),  
10 6.4-6.5 (3H, m), 6.62 (2H, d).

From the above aniline and 3-{4-[(4-*trans-tert*-butylcyclohexylamino)methyl]benzoylamino}-propionic acid methyl ester trifluoroacetate the title compound was prepared similarly as described in example 238.

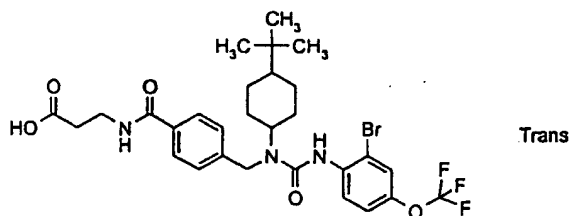
15

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.42 (2H, m), 0.62 (2H, m), 0.85 (9H, s), 0.92 (1H, m), 1.1-1.4 (5H, m), 1.9 (4H, bt), 2.70 (4H, m), 4.14 (1H, t), 4.52 (2H, s), 6.08 (1H, s), 6.77 (2H, d), 6.88 (1H, t), 7.10 (2H, d), 7.40 (2H, d), 7.76 (2H, d).

20 HPLC-MS (Method B): R<sub>t</sub> = 7.73 min, m/z = 550 (M + 1).

EXAMPLE 242 (general procedure (K))

3-{4-[3-(2-Bromo-4-trifluoromethoxyphenyl)-1-(*trans*-4-*tert*-butylcyclohexyl)ureidomethyl]-benzoylamino}propionic acid



4-Trifluoromethoxyaniline (1.0 g, 5.6 mmol) was dissolved in glacial acetic acid (10 mL). Bromine (585 μL, 11 mmol) dissolved in glacial acetic acid (2 mL) was added with stirring during 10 minutes at room temperature. The resulting mixture was stirred at room temperature for 2 hours and then poured into water (100 mL). The solid formed (2,5-dibromo-4-trifluoromethoxyaniline) was filtered off. The filtrate was made alkaline with solid sodium hy-  
30

dioxide and extracted with dichloromethane (100 mL), dried (MgSO<sub>4</sub>) and concentrated (30°C; 200 mBar) to afford 0.57 g (40%) of 2-bromo-4-trifluoromethoxyaniline.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 5.55 (2H, bs), 6.85 (1H, d), 7.10 (1H, dd), 7.37 (1H, d).

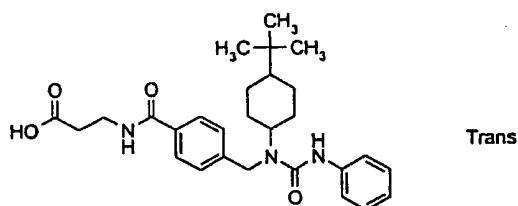
5

From the above 2-bromoaniline and 3-{4-[(4-*trans-tert*-butylcyclohexylamino)methyl]benzoylamino}propionic acid methyl ester trifluoroacetate the title compound was prepared similarly as described in example 238.

10 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.86 (9H, s), 0.95 (1H, m), 1.2 (2H, m), 1.4 (2H, m), 1.9 (4H, m), 2.74 (2H, t), 3.75 (2H, q), 4.16 (1H, t), 4.60 (2H, s), 6.85 (1H, t), 6.88 (1H, s), 7.16 (1H, dd), 7.31 (1H, d), 7.43 (2H, d), 7.76 (2H, d), 8.26 (2H, d).

EXAMPLE 243 (general procedure (K))

15 3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-phenylureidomethyl]benzoylamino}propionic acid



From 3-{4-[(4-*trans-tert*-butylcyclohexylamino)methyl]benzoylamino}propionic acid methyl ester trifluoroacetate and phenylisocyanate the title compound was prepared similarly as described in the alternative method for preparing example 92 according to the general procedure (K).

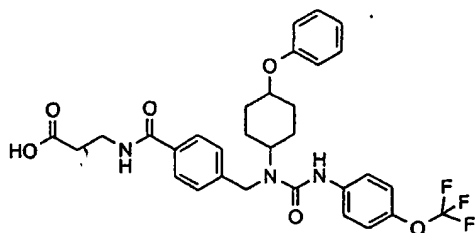
20 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.84 (9H, s), 0.93 (1H, m), 1.2 (2H, m), 1.4 (2H, m), 1.85 (4H, m), 2.63 (2H, t), 3.70 (2H, q), 4.19 (1H, t), 4.58 (2H, s), 6.75 (1H, s), 6.97 (1H, t), 7.2-7.3 (4H, m), 7.4 (3H, m), 7.80 (2H, d).

25

HPLC-MS (Method B): R<sub>t</sub> = 7.28 min, m/z = 480 (M + 1).

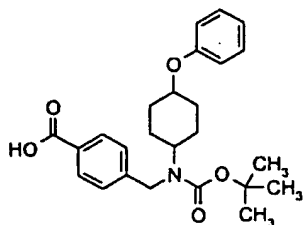
**EXAMPLE 244 (general procedure (K))**

3-{4-[1-(4-Phenoxycyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



5

Synthesis of intermediate 4-[[*tert*-butoxycarbonyl-(4-phenoxycyclohexyl)amino]methyl]-benzoic acid:



- 10 Methyl 4-(bromomethyl)benzoate (5.0 g, 22 mmol) was dissolved in DMF (50 mL) and *trans*-4-aminocyclohexanol (3.04 g, 26 mmol) was added followed by addition of potassium carbonate (6.08 g, 44 mmol). The reaction mixture was heated to 80°C for 16 hours. The reaction mixture was diluted with ethyl acetate (300 mL) and water (200 mL) was added. The aqueous phase was extracted with ethyl acetate (100 mL), and the combined organic phases were washed with water (2 x 100 mL) and dried (MgSO<sub>4</sub>). The organic phase was concentrated in vacuo to give 2.5 g of *trans*-4-[(4-hydroxycyclohexylamino)methyl]benzoic acid methyl ester.

20

HPLC-MS (method B): *m/z*: 264, *R*<sub>t</sub> = 3.48 min.

25

*trans*-4-[(4-Hydroxycyclohexylamino)methyl]benzoic acid methyl ester (2.46 g, 9.3 mmol) was suspended in sodium hydroxide (1N, 9 mL). Di-*tert*-butylpyrocarbonate (2.44 g, 11.2 mmol) dissolved in THF (11 mL) was added during 15 minutes. Additional THF (8 mL) was added and the reaction mixture was stirred for 16 hours. The reaction mixture was evaporated in vacuo until THF was removed. Water (25 mL), sodium hydroxide (1N, 1.5 mL), and diethyl ether (50 mL) was added. The water phase was extracted with diethyl ether (25 mL)

and the combined organic phases were washed with an aqueous solution of sodium hydrogensulphate (10%, 30 mL), water (3 x 20 mL), and dried (MgSO<sub>4</sub>). The organic phase was concentrated in vacuo to give 3.60 g of *trans*-4-[[*tert*-butoxycarbonyl-(4-hydroxycyclohexyl)-amino]methyl]benzoic acid methyl ester.

5

HPLC-MS (method B): m/z: 364, R<sub>t</sub> = 5.75 min.

*trans*-4-[[*tert*-Butoxycarbonyl-(4-hydroxycyclohexyl)amino]methyl]benzoic acid methyl ester (1.0 g, 2.75 mmol) was dissolved in THF (4 mL) and triphenylphosphine (1.12 g, 4.1 mmol) was added followed by addition of phenol (0.26 g, 2.75 mmol). Diethylazodicarboxylate (0.72 g, 4.1 mmol) dissolved in THF (2 mL) was added drop wise, and the reaction mixture was stirred for 16 hours. The reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography (100g silica) using ethyl acetate and heptane (1:9) as eluent to give 0.27 g of *trans*-4-[[*tert*-butoxycarbonyl-(4-phenoxy-cyclohexyl)amino]methyl]benzoic acid methyl ester. The ester was dissolved in ethanol (5 mL) and sodium hydroxide (4N, 1 mL) was added. After 5 hours the reaction mixture was concentrated in vacuo, the residue was dissolved in ethyl acetate (25 mL), and hydrochloric acid (4N, 1.3 mL) was added. The organic phase was washed with water (3 x 10 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo to give 0.25 g of *trans*-4-[[*tert*-butoxycarbonyl-(4-phenoxy-cyclohexyl)amino]methyl]benzoic acid.

10  
15  
20

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 12.85 (1H, broad), 7.90 (2H, d), 7.36 (2H, d), 7.22 (2H, t), 6.88 (3H, m), 4.53 (1H, m), 4.43 (2H, m), 2.0-1.2 (18H, m).

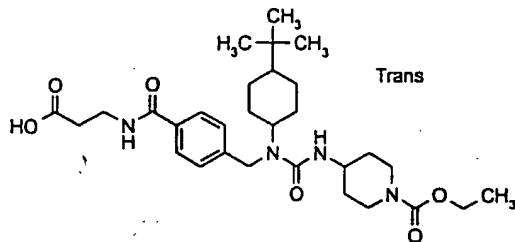
25 This intermediate was used for the synthesis the title compound.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 12.2 (1H, broad), 8.58 (2H, s), 8.48 (1H, t), 7.79 (2H, s), 7.55 (2H, s), 7.37 (2H, s), 7.25 (4H, m), 6.91 (3H, m), 4.67 (2H, s), 4.58 (1H, s), 4.24 (1H, m), 3.42 (2H, dd), 2.52-2.48 (2H, m), 2.00-1.90 (2H, m), 1.80-1.55 (4H, m), 1.50-1.40 (2H, m).

30

**EXAMPLE 245 (general procedure (K))**

4-{3-(*trans*-4-*tert*-Butylcyclohexyl)-3-[4-(2-carboxyethylcarbamoyl)benzyl]ureido}piperidine-1-carboxylic acid ethyl ester



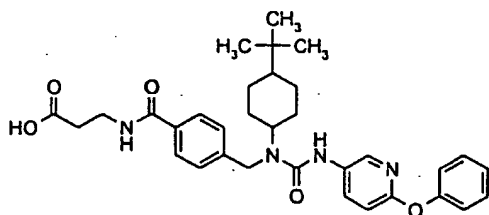
5

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 12.2 (1H, broad), 8.42 (1H, t), 7.72 (2H, d), 7.25 (2H, d), 6.02 (1H, d), 4.42 (2H, broad), 4.02 (2H, q), 3.92-3.60 (3H, m), 3.50-3.40 (2H, m), 2.90-2.70 (2H, m), 1.80-0.80 (10H, m), 0.80 (13H, s).

10

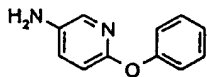
**EXAMPLE 246 (general procedure (K))**

3-[4-[1-(4-*tert*-Butylcyclohexyl)-3-(6-phenoxy pyridin-3-yl)ureidomethyl]benzoylamino]-propionic acid



15 HPLC-MS (method B): *m/z*: 573, *R*<sub>t</sub> = 7.23 min.

Synthesis of intermediate 5-amino-2-phenoxy pyridine:



- 20 Phenol (0.9 g, 9.5 mmol) was dissolved in sodium hydroxide (50% solution, 12 mL). 5-Nitro-2-chloropyridine (1.5 g, 9.5 mmol) in toluene (15 mL) was added followed by addition of tetrabutylammonium bromide (0.3 g, 0.95 mmol). The reaction mixture was stirred for 16 hours at 20°C and 5 hours at 80°C where after it was cooled to room temperature and diethyl ether (100 mL) added. The organic phase was washed with water (5 x 50 mL), dried (MgSO<sub>4</sub>), and
- 25 concentrated in vacuo to give 1.0 g of 5-nitro-2-phenoxy pyridine.

M.p. 85-87°C.

5-Nitro-2-phenoxy pyridine (0.5 g, 2.3 mmol) was added portion wise to a solution of stannous chloride (2.6 g, 12 mmol) dissolved in concentrated hydrochloric acid (10 mL) at a temperature of 0-5°C. The reaction mixture was then stirred at 20°C for 16 hours. Sodium carbonate (5 g) and aqueous ammonia (50 mL) was added. The mixture was extracted with ethyl acetate (2 x 50 mL) and the combined organic phases were washed with water (2 x 40 mL), dried (MgSO<sub>4</sub>), and concentrated in vacuo to give 0.3 g of 5-amino-2-phenoxy pyridine.

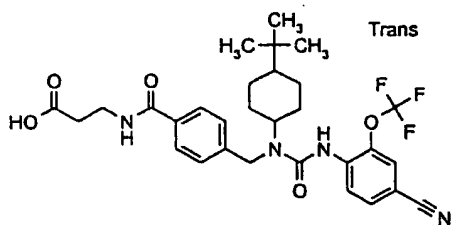
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 7.55 (1H, s), 7.33 (2H, dd), 7.08 (2H, dd), 6.93 (2H, d), 6.75 (1H, d), 5.12 (2H, broad).

This compound was transformed into the corresponding phenylcarbamate (as described for in example 237 and used in the synthesis of the title compound).

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.51 (1H, s), 8.45 (1H, broad), 8.20 (1H, d), 7.90 (1H, dd), 7.75 (2H, d), 7.35 (4H, m), 7.15 (1H, t), 7.05 (2H, d), 6.92 (1H, d), 4.57 (2H, broad), 4.02 (1H, broad), 3.40 (m), 3.38 (2H, m), 1.80-0.80 (10H, m), 0.80 (13H, s).

EXAMPLE 247 (general procedure (K))

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-cyano-2-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino}propionic acid

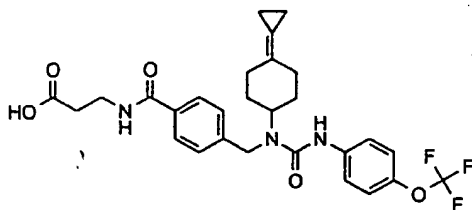


<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 12.2 (1H, broad), 8.48 (1H, t), 8.32 (1H, broad), 7.92 (1H, s), 7.90 (1H, d), 7.75 (3H, m), 7.34 (2H, d), 4.60 (2H, broad), 4.03 (1H, m), 3.45 (2H, m), 1.80-0.85 (9H, m), 0.80 (9H, s).

HPLC-MS (method B): m/z: 589, R<sub>t</sub> = 8.07 min.

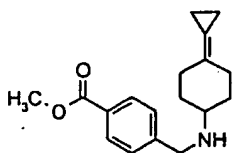
**EXAMPLE 248 (general procedure (K))**

3-{4-[1-(4-Cyclopropylidenecyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl-amino}propionic acid



5

Synthesis of intermediate 4-[(4-cyclopropylidenecyclohexylamino)methyl]benzoic acid methyl ester:



- 10 Cyclopropyltriphenylphosphonium bromide (10.8 g, 28 mmol) was suspended in dry THF (30 mL) and cooled to  $-60^{\circ}\text{C}$ . *N*-Butyllithium (1.6M in THF, 17 mL, 27 mmol) was added dropwise at  $-40$  to  $-60^{\circ}\text{C}$ . The temperature was raised to  $20^{\circ}\text{C}$  and after 3 hours at this temperature, the reaction mixture was cooled to  $-60^{\circ}\text{C}$ . 1,4-Cyclohexane dione mono ethylene ketal (4.0 g, 26 mmol) dissolved in THF (30 mL) was added at  $-60^{\circ}\text{C}$  whereafter the temperature was
- 15 raised to  $20^{\circ}\text{C}$ . After 16 hours the reaction mixture was diluted with THF (75 mL) filtered through hyflo and concentrated in vacuo. The residue was purified by flash chromatography (4 x 15 cm column of silica) using heptane and ethyl acetate (4:1) as eluent to give 2.5 g of 8-cyclopropylidene-1,4-dioxo-spiro[4.5]decane (cf Synthetic Communications 21(20), 2015-2023, 1991).

20

- Silica gel 60 (6.0 g) was suspended in dichloromethane (12 mL) and oxalic acid (10% in water, 0.6 g) was added. After 20 minutes 8-cyclopropylidene-1,4-dioxo-spiro[4.5]decane (1.6 g, 8.9 mmol) dissolved in dichloromethane (5 mL) was added and the reaction mixture was stirred for 48 hours at  $20^{\circ}\text{C}$ . Sodium hydrogen carbonate (200 mg) was added and after 1
- 25 hour the reaction mixture was filtered. The filtrate was concentrated in vacuo and the crude product of 4-cyclopropylidenecyclohexanone was used for the next step without further purification.

4-Aminomethylbenzoic acid methyl ester, hydrochloride salt (2.2 g, 11 mmol) was suspended in 1,2 dichloropropane (30 mL) and an aqueous saturated solution of potassium carbonate (15 mL) was added. The next day the organic phase was isolated and dried ( $\text{MgSO}_4$ ). 4-Cyclopropylidenecyclohexanone (1.5 g, 11 mmol) dissolved in dichloromethane (15 mL) was added followed by addition of acetic acid (400  $\mu\text{L}$ ) and sodium triacetoxymethylborohydride (3.3 g, 16.5 mmol). After 72 hours at 20°C the reaction mixture was diluted with dichloromethane (50 mL) and washed with aqueous saturated sodium hydrogen carbonate (2 x 30 mL) and water (5 x 30 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was purified by flash chromatography (50 g silica) using ethyl acetate and methanol (97:3) as eluent to give 1.1 g of 4-[(4-cyclopropylidenecyclohexylamino)methyl]benzoic acid methyl ester.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  7.90 (2H, d), 7.48 (2H, d), 3.84 (3H, s), 3.80 (2H), 3.63 (1H, m), 2.60-0.90 (12H, m).

HPLC-MS (method B):  $m/z$ : 286,  $R_t$  = 4.45 min.

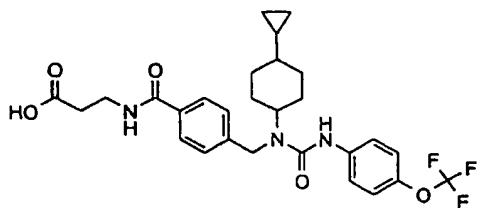
This intermediate product was used for the synthesis of the title compound.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  2.2 (1H, broad), 8.60 (1H, s), 8.43 (1H, t), 7.75 (2H, d), 7.55 (2H, d), 7.30 (2H, d), 7.22 (2H, d), 4.65 (2H, broad), 4.32 (1H, m), 3.45 (2H, m), 2.60-0.90 (14H, m).

HPLC-MS (method B):  $m/z$ : 546,  $R_t$  = 7.38 min.

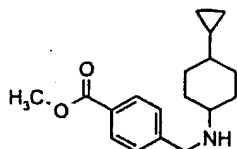
#### EXAMPLE 249 (general procedure (K))

3-{4-[1-(4-Cyclopropylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



Synthesis of intermediate 4-[(4-cyclopropylcyclohexylamino)methyl]benzoic acid methyl ester:





4-[(4-Cyclopropylidenecyclohexylamino)methyl]benzoic acid methyl ester (1.1 g, 3.9 mmol) was dissolved in DMF (40 mL) and p-toluenesulfonic acid hydrazide (2.8 g, 15.4 mmol) was added. The reaction was heated to 100°C for 16 hours. After cooling to room temperature the reaction mixture was diluted with ethyl acetate (75 mL) and water (40 mL) was added. The aqueous phase was extracted with ethyl acetate (25 mL) and the combined organic phases washed with aqueous saturated sodium hydrogen carbonate (2 x 30 mL) and water (5 x 30 mL). The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by flash chromatography (25 g silica) using heptane and ethyl acetate (1:1) as eluent to give 4-[(4-cyclopropylcyclohexylamino)methyl]benzoic acid methyl ester.

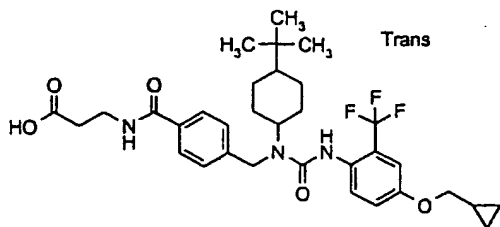
This intermediate product was used for the synthesis of the title compound.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 12.2 (1H, broad), 8.51 (1H, s), 8.43 (1H, t), 7.75 (2H, dd), 7.55 (2H, d), 7.32 (2H, dd), 7.22 (2H, d), 4.68 (1H, s), 4.60 (1H, s), 4.10 (1H, m), 3.45 (2H, dd), 1.80-0.25 (13H, m).

HPLC-MS (method B): *m/z*: 548, *R*<sub>t</sub> = 7.38 min.

#### EXAMPLE 250 (general procedure (K))

3-[4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-cyclopropylmethoxy-2-trifluoromethylphenyl)ureido-methyl]benzoylamino]propionic acid



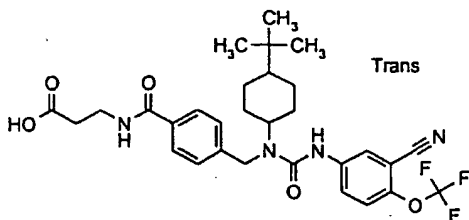
The intermediate, 4-cyclopropylmethoxy-2-trifluoromethylaniline, was prepared analogously to the aniline intermediate used in example 241.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 12.1 (1H, broad), 8.45 (1H, t), 7.98 (1H, broad), 7.75 (2H, d), 7.32 (2H, d), 7.29 (1H, s), 7.15 (2H, m), 4.52 (2H, broad), 3.88 (2H, d), 3.45 (1H, m), 1.80-0.85 (10H, m), 0.80 (9H, s), 0.60 (2H, m), 0.33 (2H, m).

5 HPLC-MS (method B): *m/z*: 618, *R*<sub>t</sub> = 6.65 min.

EXAMPLE 251 (general procedure (K))

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(3-cyano-4-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino}propionic acid

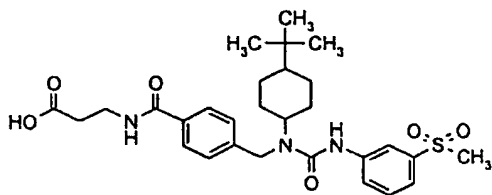


<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 12.2 (s, broad), 8.90 (1H, s), 8.43 (1H, t), 8.10 (1H, s), 7.90 (2H, dd), 7.75 (2H, d), 7.55 (1H, d), 7.32 (2H, d), 4.61 (2H, broad), 4.04 (2H, m), 3.45 (2H, m), 1.80-0.85 (10H, m), 0.80 (9H, s).

15

EXAMPLE 252 (general procedure (K))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-methylsulfonylphenyl)ureidomethyl]benzoylamino}-propionic acid



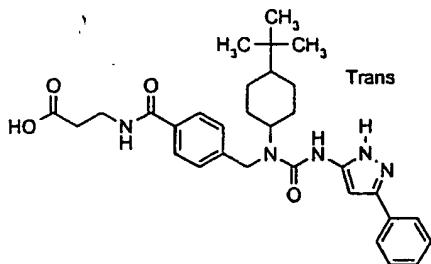
The title compound was prepared from the corresponding 3-methylsulfonyl compound (general procedure (K)) followed by oxidation of the sulfanyl group and hydrolysis of the propionic acid ester.

25 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 12.2 (s, broad), 8.76 (1H, s), 8.45 (1H, t), 8.07 (1H, s), 7.83 (1H, d), 7.74 (2H, d), 7.50 (2H, m), 7.30 (2H, d), 4.60 (2H, broad), 4.08 (2H, d), 3.45 (2H, t), 3.18 (3H, s), 2.50 (2H, t), 1.80-0.85 (9H, m), 0.80 (9H, s).

HPLC-MS (method B):  $m/z$ : 558,  $R_t$  = 6.52 min.

EXAMPLE 253 (general procedure (K))

- 5 3-{4-[1-(4-*trans*-*tert*-Butylcyclohexyl)-3-(5-phenyl-2*H*-pyrazol-3-yl)ureidomethyl]-benzoylamino}propionic acid



Using isocyanate formed in situ from 5-amino-3-phenylpyrazole and triphosgene:

- 10 To a suspension of 5-amino-3-phenylpyrazole (183 mg, 8.7 mmol) in 1,2-dichloroethane (5 mL) was added *N,N*-diisopropylethylamine (0.2 mL, 1.2 mmol) followed by addition of triphosgene (115 mg, 0.38 mmol). The solution was heated to reflux for two hours. To this mixture a solution of 3-{4-[1-(4-*trans*-*tert*-butylcyclohexylamino)methyl]benzoylamino}propionic acid methyl ester trifluoroacetate (350 mg, 0.70 mmol) and *N,N*-diisopropylethylamine (0.2 mL, 1.2 mmol) in DMF (4 mL) was added and stirring at 80°C was continued for 2 hours. The mixture was allowed to cool to room temperature, poured into water (50 mL) and the water phase was washed ethyl acetate (2 x 50 mL). The combined organic phases were concentrated in vacuo and purification on silica column with dichloromethane/methanol (95:5) afforded the 3-{4-[1-(4-*trans*-*tert*-butylcyclohexyl)-3-(5-phenyl-2*H*-pyrazol-3-yl)ureidomethyl]-benzoylamino}propionic acid methyl ester as a solid which was redissolved in ethanol (4 mL). Sodium hydroxide (1 mL, 4 N) was added and the reaction mixture was left at room temperature for 30 min. Hydrochloric acid (4 mL, 1 N) was added, and the resulting precipitate was subsequently collected by filtration. Recrystallisation from acetonitrile afforded the title compound.

25

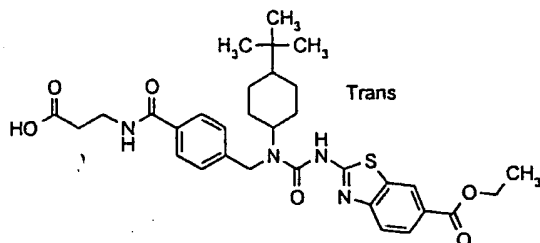
<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  0.82 (9H, s), 0.9-1.5 (5H, m), 1.69 (4H, bt), 4.09 (1H, bt), 4.58 (2H, s), 6.64 (1H, s), 7.25-7.50 (5 H, m), 7.60-7.80 (4H, m), 8.50 (1H, t), 9.0 (1H, s).

HPLC-MS (Method B):  $R_t$  = 6.52 min,  $m/z$  = 546 (M+1).

30

**EXAMPLE 254 (general procedure (K))**

**2-{3-(4-*trans-tert*-Butylcyclohexyl)-3-[4-(2-carboxyethylcarbamoyl)benzyl]ureido}-benzothiazole-6-carboxylic acid ethyl ester**



5

Using isocyanate formed in situ from (substituted) 2-aminobenzothiazole and diphosgene in pyridine:

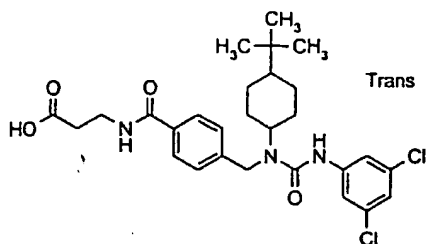
Ethyl-2-aminobenzothiazole-6-carboxylate (262 mg, 1.2 mmol) was suspended in pyridine (4 ml). Diphosgene (80  $\mu$ L, 0.66 mmol) was added and the solution was stirred for two hours at room temperature. To this mixture a solution of 3-{4-[(4-*trans-tert*-butylcyclohexylamino)-methyl]benzoylamino}propionic acid methyl ester trifluoroacetate (300 mg, 0.61 mmol) and *N,N*-diisopropylethylamine (0.4 mL, 2.4 mmol) in DMF (4 mL) was added and stirring at 80°C was continued for 2 hours. The mixture was allowed to cool to room temperature and poured into acetonitrile (50 mL), the resulting precipitate was filtered off and the filtrate was then partitioned between ethyl acetate (50 mL) and hydrochloric acid (2 x 50 mL, 1 N). The organic phase was concentrated in vacuo to give an oil which was redissolved in ethanol (4 mL). Sodium hydroxide (1 mL, 4 N) was added and the reaction mixture was left at room temperature for 30 min. Hydrochloric acid (4 mL, 1 N) was added, and the resulting precipitate was subsequently collected by filtration to afford the title compound.

20

HPLC-MS (Method B):  $R_t$  = 7.65 min,  $m/z$  = 609 ( $M^+$ ).

EXAMPLE 255 (general procedure (K))

3-[4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino]-propionic acid



5

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 12.2 (s, 1H), 8.68 (s, 1H), 8.45 (t, 1H), 7.74 (d, 2H), 7.61 (s, 2H), 7.30 (d, 2H), 7.11 (s, 1H), 4.57 (s, 2H), 4.02 (m, 1H), 3.43 (m, 2H), 2.50 (m, 2H), 1.8-0.75 (m, 9H), 0.80 (s, 9H)

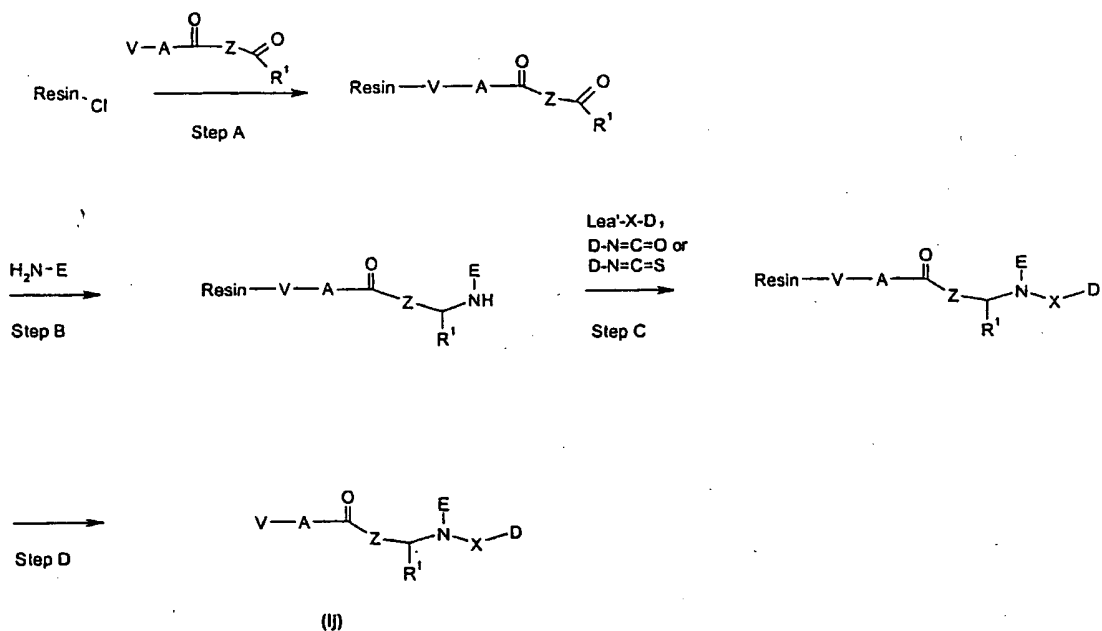
10 HPLC-MS (method B): *m/z*: 548, *R*<sub>t</sub> = 8.35min

MA: Calc for C<sub>28</sub>H<sub>35</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>4</sub>:

61.31% C, 6.43% H, 7.66% N; Found

61.20% C, 6.59% H, 7.34% N.

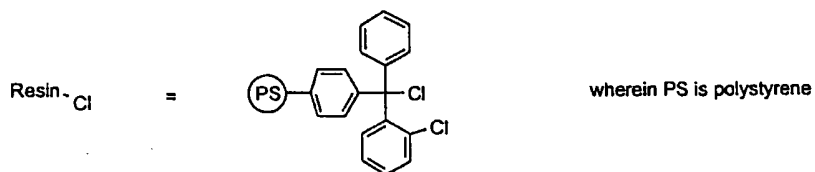
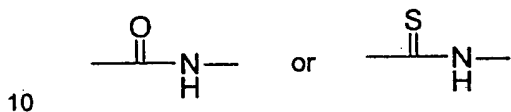
General procedure (L) for the solid phase synthesis of compounds of the general formula (II):



5 wherein

A, V, Z, R<sup>1</sup>, E and D are as defined for formula (I),

X is



, and

Lea' is a leaving group such as -OSu, chloro, phenoxy, or 4-nitrophenoxy.

Step A:

The reaction is known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 24) and is generally performed by shaking a suspension of the resin with a solution of V-A-Z-C(O)R<sup>1</sup> in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine. Typical solvents are pyridine, dichloromethane, 1,2-dichloroethane, DMF, NMP, THF, DMSO or mixtures of two or more of these. The reaction is performed between 20°C and 120°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed with any solvent mentioned above including mixtures hereof, containing a base as mentioned above and an alcohol, typically methanol, as a scavenger of unreacted resin bound 2-chlorotriylchloride.

Step B:

Step B is identical to step C of general procedure (T).

Step C:

Step C is identical to step D of general procedure (T).

Step D:

Step D is identical to step E of general procedure (T).

Preparation of starting materials D-N=C=O:N,N-Dimethyl-3-nitro-benzenesulfonamide

3-Nitrobenzenesulfonyl chloride (22.8 mmol, 5.05 g) was dissolved in dry THF (50 mL). Dimethylamine in THF (2M, 34 mL) was added and the mixture was refluxed for 2 hours. Upon cooling, the mixture was filtered and the filtrate was evaporated in vacuo. The residue was dissolved in ethyl acetate (250 mL), washed with water (3 x 50 mL) and dried over MgSO<sub>4</sub>. Evaporation of the solvent afforded the title compound.

1-(3-Nitrobenzenesulfonyl)piperidine was prepared as described above using piperidine instead of dimethylamine.

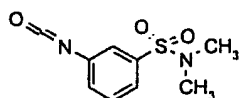
3-Amino-N,N-dimethylbenzenesulfonamide

To a solution of the above N,N-dimethyl-3-nitro-benzenesulfonamide (20.4 mmol, 4.7 g) in ethanol (50 mL) was added SnCl<sub>2</sub> (105 mmol, 19.9 g) and the mixture was refluxed for 1

hour. Upon cooling, the solvent was removed in vacuo. Ethyl acetate (200 mL) and NaHCO<sub>3</sub> (sat, 100 mL) were added to the residue followed by another 200 mL ethyl acetate and 500 mL water. The phases were separated and the organic phase was washed twice with water. The organic phase was filtered, washed with water (2 x 100 mL) dried over MgSO<sub>4</sub> and  
5 evaporated to leave the title compound.

3-(Piperidine-1-sulfonyl)phenylamine was prepared as described above from 1-(3-nitrobenzenesulfonyl)piperidine.

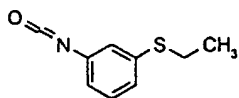
10 3-Isocyanato-*N,N*-dimethylbenzenesulfonamide



To a slurry of the above 3-amino-*N,N*-dimethylbenzenesulfonamide (3.26 g, 16 mmol) in toluene (200 mL) was added triphosgene (1.67 g) and the mixture was refluxed 16 h and  
15 evaporated. The residue was used without further purification.

1-(3-Isocyanatobenzenesulfonyl)piperidine was prepared as described above from 3-piperidine-1-sulfonyl)phenylamine.

20 1-Ethylsulfanyl-3-isocyanatobenzene



To a solution of 3-aminothiophenol (40 mmol, 5 g) in DMF (50 mL) was added K<sub>2</sub>CO<sub>3</sub> (4.8 mmol, 6.63 g) and 2.98 mL bromoethane. The mixture was stirred over night at 25°C and  
25 poured into 200 mL ice water. 200 mL ethylacetate was added and the phases were separated. The aqueous phase was extracted with 100 mL ethylacetate and the combined organic extracts were dried over MgSO<sub>4</sub>. Evaporation of the solvent and re-dissolving the residue in ethyl acetate (100 mL) and HCl in ethyl acetate (2M, 20 mL) afforded 3-ethylsulfanylphenylamine hydrochloride, which was collected by filtration.

30

To a slurry of the above 3-ethylsulfanylphenylamine hydrochloride (31.6 mmol, 6 g) in toluene (100 mL) was added diphosgene (trichloromethyl chloroformate, 158 mmol, 31.3 g) and

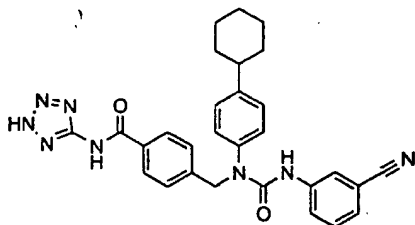


the mixture was refluxed for 2 hours affording a clear solution. The solvent was removed in vacuo and the residue was used without further purification.

The other starting materials used in the following examples were prepared in a similar way.

5 EXAMPLE 256 (general procedure (L))

4-[3-(3-Cyanophenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



10 Step A: Resin bound 4-formyl-N-(2H-tetrazol-5-yl)benzamide

150  $\mu$ mol 4-Formyl-N-(2H-tetrazol-5-yl)benzamide was dissolved in a mixture of 250  $\mu$ L dichloromethane, 250  $\mu$ L DMF and 100  $\mu$ L diisopropylethylamine and added to 50 mg polystyrene resin functionalized with a 2-chlorotriyl chloride linker. After shaking the suspension for 4 hours at 25°C, the resin was isolated by filtration and washed with 2 x 1 mL dichloromethane: methanol:diisopropylethylamine 17:2:1 and 2 x 1 mL DMF.

Step B: Resin bound 4-[(4-cyclohexylphenylamino)methyl]-N-(2H-tetrazol-5-yl)benzamide

The above resin bound 4-formyl-N-(2H-tetrazol-5-yl)benzamide (50 mg) was treated with a 0.5 M solution of 4-cyclohexylaniline (0.25 mmol, 41.25 mg) in a mixture of DMF and trimethylorthoformate (1:1, 0.5 mL) and glacial acetic acid (50  $\mu$ L) for 1 hour at 25°C followed by sodium cyanoborohydride (250  $\mu$ mol, 16 mg) dissolved in a mixture of DMF and methanol (1:1, 0.25 mL). Shaking at 25°C for 4 hours followed by filtration and washing with a mixture of DMF and methanol (1:1, 2x1 mL), 3 x 1 mL DMF and 2 x 1 mL dichloromethane afforded the desired product.

25 Step C: Resin bound 4-[3-(3-cyanophenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

200  $\mu$ mol 3-cyanophenylisocyanate dissolved in 500  $\mu$ L dichloroethane was added to the above resin bound 4-[(4-cyclohexylphenylamino)methyl]-N-(2H-tetrazol-5-yl)benzamide (50 mg). Shaking the mixture for 5 hours at 25°C followed by filtration and washing of the resin with 2 x 1 mL dichloromethane, 4 x 1 mL DMF, 2 x 1 mL H<sub>2</sub>O, 3 x 1 mL THF and 3 x 1 mL dichloromethane afforded the resin bound title compound.

Step D: 4-[3-(3-Cyanophenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide

The above resin bound 4-[3-(3-cyanophenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide (50 mg) was treated with 1 mL 5% TFA in dichloromethane for 1 hour at 25°C. The product was filtered off and the resin was washed with 1 mL dichloromethane. The combined extracts were concentrated in vacuo. The residue was dissolved in 50 µL DMSO + 500 µL acetonitrile and purified by preparative HPLC using a Supelcosil ABZ+ 25 cm x 10 mm 5µ column. The starting eluent composition was 5% acetonitrile in water changing over 30 min to 90% acetonitrile in water which was then kept constant for 5 min before going back to the starting composition over 10 min. The flow rate was kept constant at 8 mL/min collecting one fraction per minute. The process was monitored using a UV detector operating at 214 nm. The fractions containing the desired product were combined and evaporated in vacuo to afford the title compound.

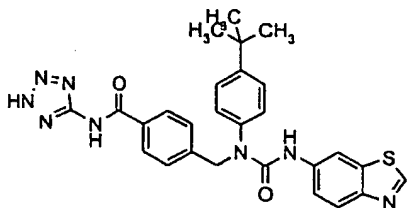
Optionally, the compound can be purified by recrystallisation from eg acetonitrile.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 12.35 (s br, 1H); 8.58 (s, 1H); 8.05 (d, 2H); 7.95 (s, 1H); 7.73 (d, 1H); 7.50-7.38 (m, 4H); 7.20 (s, 4H); 5.00 (s, 2H); 1.85-1.60 (m, 5H); 1.45-1.10 (m, 6H).

HPLC-MS (method B): *m/z* = 521, *R*<sub>t</sub> = 7.60 min.

EXAMPLE 257 (general procedure (L))

4-[3-Benzothiazol-6-yl]-1-(4-*tert*-butylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

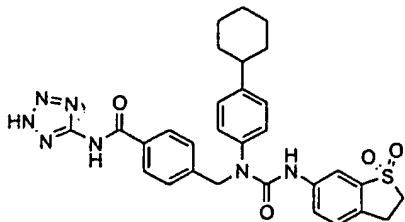


<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.5 (s, 1H); 8.28 (s, 1H); 8.05 (d, 2H); 7.93 (d, 2H); 7.55 (d, 1H); 7.48 (d, 2H); 7.43 (d, 2H); 7.22 (d, 2H); 5.03 (s, 2H); 1.28 (s, 9H).

HPLC-MS (Method B): *m/z* = 527 (*M*+1). *R*<sub>t</sub> = 6.47 min.

EXAMPLE 258 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(1,1-dioxo-2,3-dihydro-1H-1-benzo[b]thiophen-6-yl)ureido-methyl]-N-(2H-tetrazol-5-yl)benzamide



5

The benzothiophene moiety was synthesized from commercially available 6-amino-1,1-dioxo-1H-1-benzo[b]thiophene using Pd/C and H<sub>2</sub> employing methods known by those skilled in the art. The aniline was converted to an isocyanate by methods mentioned previously.

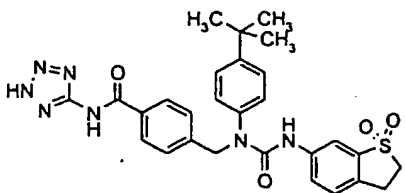
10

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 12.40 (s, 1H); 8.60 (s, 1H); 8.05 (s, 2H); 7.88 (s, 1H); 7.68 (d, 1H); 7.45 (d, 2H); 7.39 (d, 1H); 7.20 (s, 4H); 5.00 (s, 2H); 3.58 (t, 2H); 3.30 (t, 2H); 1.85-1.65 (m, 5H); 1.50-1.15 (m, 5H).

15 HPLC-MS (Method B): m/z = 586 (M+1). R<sub>t</sub> = 7.88 min.

EXAMPLE 259 (general procedure (L))

4-[1-(4-tert-Butylphenyl)-3-(1,1-dioxo-2,3-dihydro-1H-benzo[b]thiophen-6-yl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



20

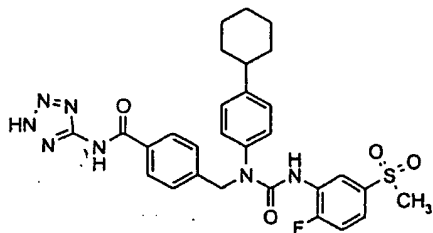
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 12.40 (s, 1H); 8.65 (s, 1H); 8.05 (s, 2H); 7.88 (s, 1H); 7.60 (d, 1H); 7.48 (d, 2H); 7.45-7.38 (m, 3H); 7.22 (d, 2H); 5.00 (s, 2H); 3.58 (t, 2H); 3.34 (t, 2H); 1.32 (s, 9H).

25

HPLC-MS (Method B): m/z = 560 (M+1). R<sub>t</sub> = 7.58 min.

EXAMPLE 260 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(2-fluoro-5-methylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

2-Fluoro-5-methylsulfonylphenyl isocyanate was prepared from the corresponding 2-fluoro-5-methylsulfonyl-1-nitrobenzene via reduction to the corresponding aniline as described previously.

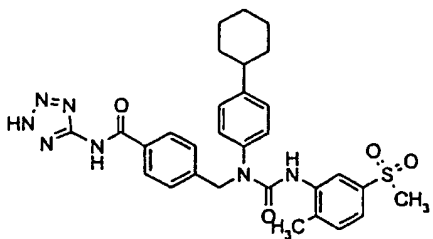
10 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 11.50 (s br, 1H); 8.30 (d, 1H); 8.00 (d, 2H); 7.90 (s, 1H); 7.65 (m, 1H); 7.50-7.40 (m, 3H); 7.25 (s, 4H); 5.05 (s, 2H); 3.18 (s, 3H); 1.85-1.65 (m, 5H); 1.50-1.15 (m, 5H).

HPLC-MS (Method B): *m/z* = 592 (M+1). *R*<sub>t</sub> = 7.04 min.

15

EXAMPLE 261 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(5-methylsulfonyl-2-methylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



20

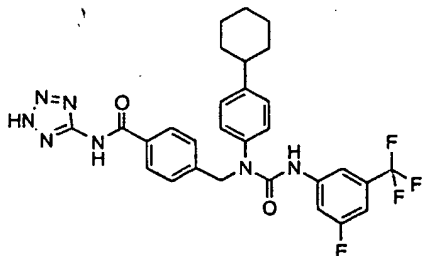
5-Methylsulfonyl-2-methylphenyl isocyanate was prepared from the corresponding 5-methylsulfonyl-2-methyl-1-nitrobenzene via reduction to the corresponding aniline followed by conversion to the isocyanate as described previously.

25 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 12.10 (s br, 1H); 8.15 (s, 1H); 8.05 (d, 2H); 7.62 (m, 6H); 7.28 (dd, 4H); 5.03 (s, 2H); 3.15 (s, 3H); 2.10 (s, 3H); 1.85-1.65 (m, 5H); 1.50-1.15 (m, 5H).

HPLC-MS (Method B):  $m/z$  = 588 (M+1).  $R_t$  = 7.10 min.

EXAMPLE 262 (general procedure (L))

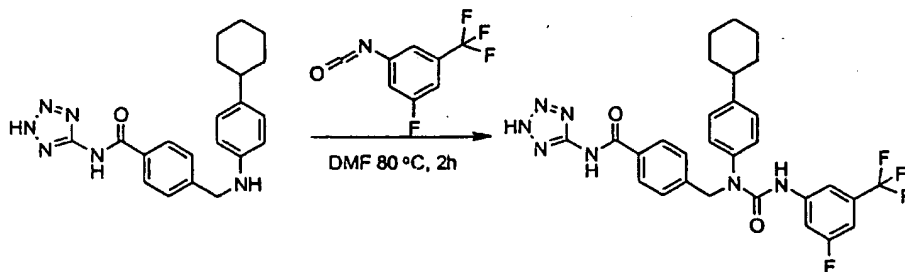
- 5 4-[1-(4-Cyclohexylphenyl)-3-(3-fluoro-5-trifluoromethylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



- $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  12.40 (s, 1H); 8.82 (s, 1H); 8.08 (d, 2H); 7.75 (m, 2H); 7.45 (d, 2H);  
10 7.25-7.15 (m, 5H); 5.02 (s, 2H); 1.85-1.65 (m, 5H); 1.50-1.15 (m, 5H).

HPLC-MS (Method B):  $m/z$  = 582 (M+1).  $R_t$  = 8.05 min.

Alternative method for the preparation of the title compound:



15

Preparation of 3-fluoro-5-trifluoromethylphenylisocyanate:

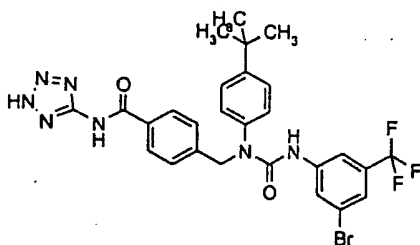
- 3-Fluoro-5-trifluoromethylaniline (2 g, 11.2 mmol) was dissolved in 20 mL diethylether and  
added concentrated hydrochloric acid (37%, 1.5 mL, 18 mmol). Upon stirring for 1 hour at  
20 25°C the solvent was removed in vacuo and the white solid was stripped with toluene (3 x 20  
mL). Diphosgene (20 mL) was added to the hydrochloride salt and the mixture was refluxed  
over night. Excess diphosgene was removed in vacuo and the clear oil was stripped with  
toluene (3 x 20 mL). The obtained isocyanate was used without further purification.

Preparation of 4-[1-(4-Cyclohexylphenyl)-3-(3-fluoro-5-trifluoromethylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide:

A slurry of 4-[(4-cyclohexylphenylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide (3 g, 7.96 mmol) in DMF (50 mL) was added to the above 3-fluoro-5-trifluoromethylphenylisocyanate and the mixture was heated to 80°C. After 2 hours the reaction was allowed to cool to 25°C and acetonitrile (500 mL) was added. The mixture was filtered, the precipitate was discarded and the filtrate evaporated. The residue was refluxed in acetonitrile (75 mL) and allowed to cool to 25°C. After filtration, a new precipitate was formed affording the title compound (850 mg).

EXAMPLE 263 (general procedure (L))

4-[3-(3-Bromo-5-trifluoromethylphenyl)-1-(4-*tert*-butylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

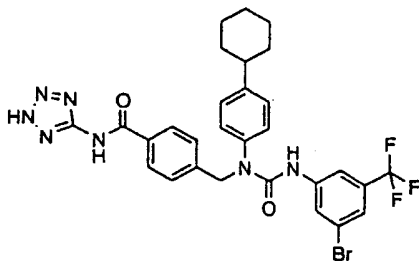


HPLC-MS (Method B):  $m/z$  = 617 ( $M+1$ ).  $R_t$  = 7.95 min.

$^1\text{H}$  NMR (DMSO):  $\delta$  12.40 (s, 1H); 8.80 (s, 1H); 8.10 (s, 1H); 8.04 (d, 2H); 7.92 (s, 1H); 7.50 (s, 1H); 7.49 (d, 2H); 7.42 (d, 2H); 7.23 (d, 2H); 5.02 (s, 2H); 1.32 (s, 9H).

EXAMPLE 264 (general procedure (L))

4-[3-(3-Bromo-5-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



HPLC-MS (Method B):  $m/z = 642$  ( $M+1$ ).  $R_t = 8.45$  min.

Alternative method for the preparation of the title compound:

5 Preparation of 3-bromo-5-trifluoromethylphenylisocyanate:

3-Bromo-5-trifluoromethylaniline (2.16 g, 9 mmol) was dissolved in 20 mL diethylether and added concentrated hydrochloric acid (37%, 1.5 mL, 18 mmol). Upon stirring for 1 hour at 25°C the solvent was removed in vacuo and the white solid was stripped with toluene (3 x 20 mL). Diphosgene (13 mL) was added to the ammonium chloride salt and the mixture was re-  
10 fluxed for 3.5 hours until no solid material precipitated on cooling. Excess diphosgene was removed in vacuo and the clear oil was stripped with toluene (3 x 20 mL). The obtained isocyanate was used without further purification.

15 Preparation of 4-[3-(3-bromo-5-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide:

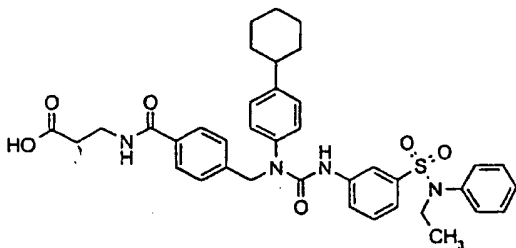
The above isocyanate was dissolved in DMF (20 mL) and added 4-[(4-cyclohexylphenyl-amino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide (1.88 g, 5 mmol) and the mixture was heated at 80°C. After 1 hour the reaction was allowed to cool to 25°C and the solvent was evapo-  
20 rated. The residue was refluxed in acetonitrile (10 mL) and allowed to cool to 25°C. The desired product was isolated by filtration and dried in vacuo (2.5 g).

<sup>1</sup>H NMR (DMSO):  $\delta$  12.35 (s, 1H); 8.75 (s, 1H); 8.10 (s, 1H); 8.04 (d, 2H); 7.92 (s, 1H); 7.50 (s, 1H); 7.48 (d, 2H); 7.23 (s, 4H); 5.00 (s, 2H); 1.85-1.65 (m, 5H); 1.45 -1.15 (m, 5H).

25 HPLC-MS (Method F):  $m/z = 642$  ( $M+1$ ).  $R_t = 5.67$  min.

EXAMPLE 265 (general procedure (L))

3-(4-{1-(4-Cyclohexylphenyl)-3-[3-(ethylphenylsulfamoyl)phenyl]ureidomethyl}benzoylamino)-propionic acid



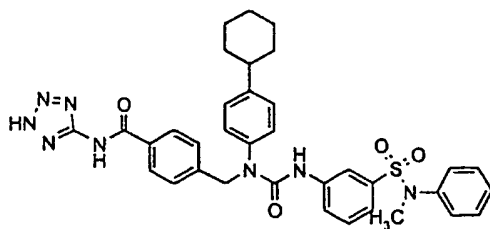
5

HPLC-MS (Method B):  $m/z$  = 683 ( $M+1$ ).  $R_t$  = 7.60 min.

EXAMPLE 266 (general procedure (L))

4-{1-(4-Cyclohexylphenyl)-3-[3-(methylphenylsulfamoyl)phenyl]ureidomethyl}-N-(2H-tetrazol-5-yl)benzamide

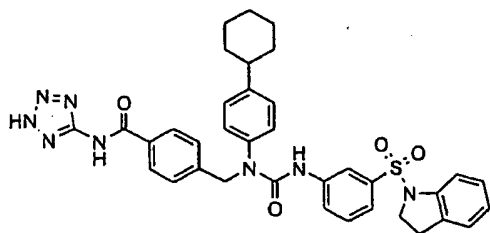
10



HPLC-MS (Method B):  $m/z$  = 665 ( $M+1$ ).  $R_t$  = 7.67 min.

15 EXAMPLE 267 (general procedure (L))

4-{1-(4-Cyclohexylphenyl)-3-[3-(2,3-dihydroindole-1-sulfonyl)phenyl]ureidomethyl}-N-(2H-tetrazol-5-yl)benzamide

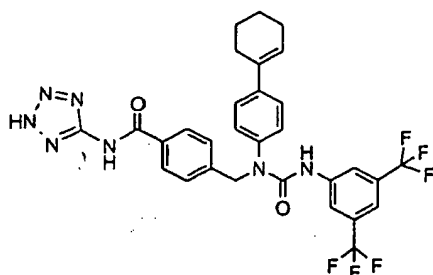


20 HPLC-MS (Method B):  $m/z$  = 677 ( $M+1$ ).  $R_t$  = 7.75 min.



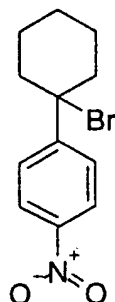
EXAMPLE 268 (general procedure (L))

4-[3-(3,5-Bis-trifluoromethylphenyl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

The starting material 4-(cyclohex-1-enyl)phenylamine was prepared in the following way:

Step 1: 1-(1-Bromocyclohexyl)-4-nitrobenzene

10

4-Cyclohexylnitrobenzene (22.6 g, 0.11 mol) and *N*-bromosuccinimide (21.6 g, 0.12 mol) were suspended in tetrachloromethane (200 mL) and a catalytic amount of dibenzoylperoxide was added. The reaction mixture was stirred at 80°C for 4.5 hours. The reaction mixture was concentrated in vacuo and the residue dissolved in ethyl acetate (400 mL) and washed with water (100 mL). The aqueous phase was extracted with ethyl acetate (200 mL) and the combined organic phases were washed with water (3 x 150 mL), dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue was crystallised from ethyl acetate and heptane to give 18.4 g of 1-(bromocyclohexyl)-4-nitrobenzene.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.29-1.40 (1H,m), 1.60-1.71 (3H,d), 1.73-1.85 (2H,m), 2.06-2.18 (2H,m), 2.55 (2H,m), 7.92 (2H,d), 8.34 (2H,d).

M.p.: 83.5-85.5°C.

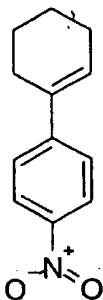
MA: calc

50.72% C, 4.97% H, 4.93% N; Found

50.65% C, 5.10% H, 4.91% N.

5

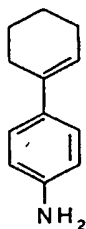
Step 2: 1-Cyclohex-1-enyl-4-nitrobenzene



1-(Bromocyclohexyl)-4-nitrobenzene (18.4 g, 64.8 mmol), lithium carbonate (5.3 g, 71.2 mmol), and lithium bromide (6.2 g, 71.2 mmol) were reacted together in DMF (100 mL) for 2 hours at 160°C. The reaction mixture was cooled to 20°C, diluted with ethyl acetate (500 mL), and washed with water (300 mL). The aqueous phase was extracted with ethyl acetate (200 mL) and the combined organic phases were washed with water (3 x 150 mL), dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue was purified on silica (350 g) using ethyl acetate and heptane (1:9) as eluent to give 11.7 g of 1-cyclohex-1-enyl-4-nitrobenzene.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.57-1.69 (2H,m), 1.60-1.70 (2H,m), 2.18-2.29 (2H,m), 2.38-2.46 (2H,m), 6.46 (1H,t), 7.67 (2H,d), 8.17 (2H,d).

20 Step 3: 4-(Cyclohex-1-enyl)phenylamine



1-Cyclohex-1-enyl-4-nitrobenzene (11.7 g, 57.6 mmol) was dissolved in hot absolute ethanol (170 mL). Stannous chloride (65 g, 288 mmol) was added and the reaction mixture was

stirred at reflux temperature for 1.5 hours. The reaction mixture was concentrated in vacuo and the residue was added ethyl acetate (700 mL) and water (700 mL), and neutralised to pH 7 with sodium hydroxide (4 N). Ethyl acetate (150 mL) was added and the mixture was filtered through celite. The organic phase of the filtrate was washed with water and a saturated solution of sodium chloride, dried over  $\text{MgSO}_4$ , and concentrated in vacuo. The residue was purified on silica (200 g) using ethyl acetate and heptane (1:4) as eluent to give 7.4 g of 4-(cyclohex-1-enyl)phenylamine.

HPLC-MS (method B):  $m/z$ : 174,  $R_t$  = 4.05 min.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.52-1.60 (2H,m), 1.63-1.72 (2H,m), 2.13 (2H,m), 2.28 (2H,m), 5.0 (2H,s), 5.90 (1H,t), 6.50 (2H,d), 7.08 (2H,d).

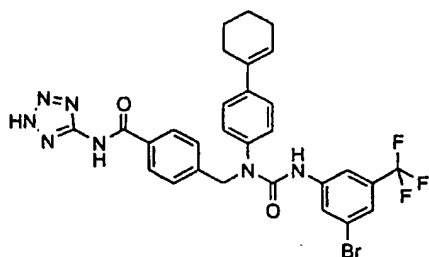
The title compound was prepared using 4-(cyclohex-1-enyl)phenylamine in step B.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  12.40 (s, 1H); 8.92 (s, 1H); 8.28 (s, 2H); 8.04 (d, 2H); 7.61 (s, 1H); 7.48 (d, 2H); 7.46 (d, 2H); 7.25 (d, 2H); 6.20 (s br, 1H); 5.03 (s, 2H); 2.38 (m br, 2H); 2.18 (m br, 2H); 1.71 (m br, 2H); 1.60 (m br, 2H).

HPLC-MS (Method B):  $m/z$  = 630 ( $M+1$ ).  $R_t$  = 8.25 min.

#### EXAMPLE 269 (general procedure (L))

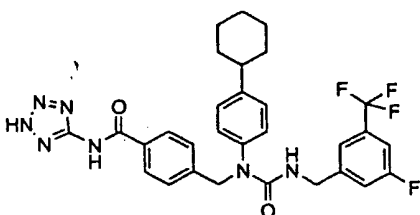
4-[3-(3-Bromo-5-trifluoromethylphenyl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



HPLC-MS (Method B):  $m/z$  = 641 ( $M+1$ ).  $R_t$  = 8.27 min.

EXAMPLE 270 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(3-fluoro-5-trifluoromethylbenzyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

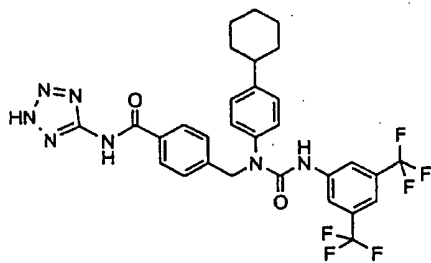


$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  12.40 (s, 1H); 8.04 (d, 2H); 7.53 (d, 1H); 7.45 (s, 1H); 7.38 (d, 2H); 7.24 (d, 2H); 7.12 (d, 2H); 6.69 (t, 1H); 4.90 (s, 2H); 4.30 (d, 2H); 1.80-1.65 (m, 5H); 1.50-1.15 (m, 5H).

HPLC-MS (Method B):  $m/z$  = 596 ( $M+1$ ).  $R_t$  = 7.70 min.

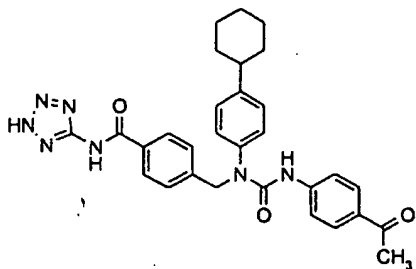
EXAMPLE 271 (general procedure (L))

4-[3-(3,5-Bis-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  12.40 (s br, 1H); 8.95 (s, 1H); 8.25 (s, 2H); 8.05 (d, 2H); 7.62 (s, 1H); 7.45 (d, 2H); 7.24 (s, 4H); 5.02 (s, 2H); 1.82-1.65 (m, 5H); 1.50-1.15 (m, 5H)

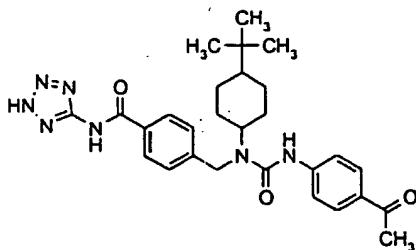
HPLC-MS (Method B):  $m/z$  = 632 ( $M+1$ ).  $R_t$  = 8.37 min.

**EXAMPLE 272 (general procedure (L))**4-[3-(4-Acetylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

- 5  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  12.35 (s br, 1H); 8.62 (s, 1H); 8.05 (d, 2H); 7.85 (d, 2H); 7.60 (d, 2H); 7.45 (d, 2H); 7.20 (s, 4H); 5.00 (s, 2H); 1.85-1.60 (m, 5H); 1.45-1.10 (m, 6H).

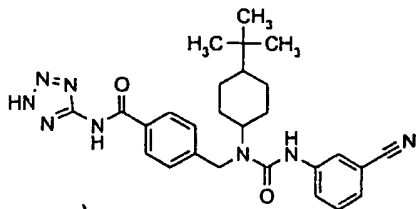
HPLC-MS (method B):  $m/z$  = 538,  $R_t$  = 7.42 min.

10 **EXAMPLE 273 (general procedure (L))**

4-[3-(4-Acetylphenyl)-1-(4-*tert*-butylcyclohexyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

- 15  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  12.35 (s br, 1H); 8.85 (s, 1H); 8.05 (d, 2H); 7.85 (d, 2H); 7.62 (d, 2H); 7.43 (d, 2H); 4.70 (s, 2H); 4.10 (t br, 1H); 1.85-0.90 (m, 9H); 0.85 (s, 9H).

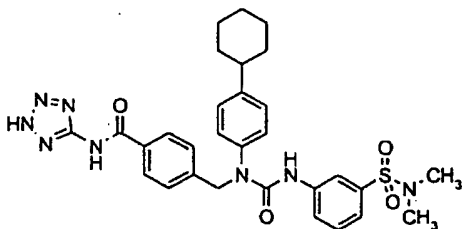
HPLC-MS (method B):  $m/z$  = 518,  $R_t$  = 7.35 min.

EXAMPLE 274 (general procedure (L))4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-cyanophenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

- 5  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  12.30 (s br, 1H); 8.73 (s, 1H); 8.05 (d, 2H); 7.93 (s, 1H); 7.75 (d, 1H); 7.50-7.30 (m, 4H); 4.65 (s, 2H); 4.08 (t br, 1H); 1.83-0.90 (m, 9H); 0.85 (s, 9H).

HPLC-MS (method B):  $m/z$  = 501,  $R_t$  = 7.62 min.

10 EXAMPLE 275 (general procedure (L))

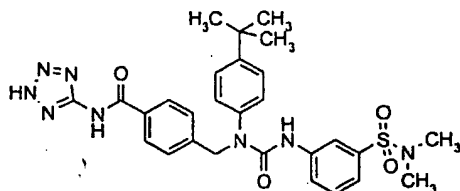
4-[1-(4-Cyclohexylphenyl)-3-(3-dimethylsulfamoylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

- 15  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  12.40 (s br, 1H); 8.70 (s, 1H); 8.05 (d, 2H); 7.90 (s, 1H); 7.73 (d, 1H); 7.50-7.40 (m, 3H); 7.30 (d, 1H); 7.20 (s, 4H); 5.00 (s, 2H); 2.60 (s, 6H) 1.85-1.60 (m, 5H); 1.45-1.10 (m, 6H).

HPLC-MS (method B):  $m/z$  = 603,  $R_t$  = 7.08 min.

EXAMPLE 276 (general procedure (L))

4-[1-(4-*tert*-Butylphenyl)-3-(3-dimethylsulfonylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



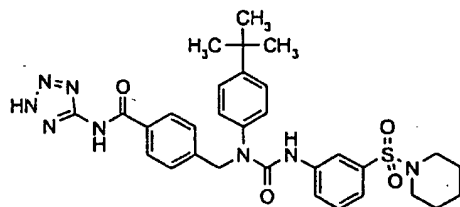
5

<sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 12.40 (s br, 1H); 8.70 (s, 1H); 8.05 (d, 2H); 7.90 (t, 1H); 7.70 (d, 1H); 7.55-7.35 (m, 5H); 7.30 (d, 1H); 7.23 (d, 2H); 5.00 (s, 2H); 2.60 (s, 6H) 1.28 (s, 9H).

10 HPLC-MS (method B): *m/z* = 577, *R*<sub>t</sub> = 6.48 min.

EXAMPLE 277 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-[3-(piperidine-1-sulfonyl)phenyl]ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



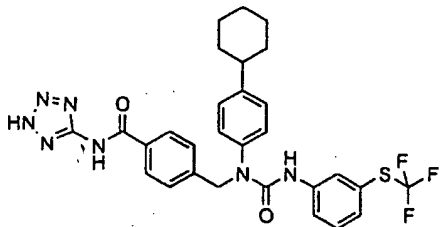
15

<sup>1</sup>H NMR (300 MHz), (DMSO-*d*<sub>6</sub>): δ 12.40 (s br, 1H); 8.70 (s, 1H); 8.05 (d, 2H); 7.90 (s, 1H); 7.70 (d, 1H); 7.52-7.18 (m, 8H); 5.00 (s, 2H); 2.90 (t, 4H) 1.65-1.35 (m, 6H); 1.28 (s, 9H).

20 HPLC-MS (method B): *m/z* = 617, *R*<sub>t</sub> = 7.22 min.

**EXAMPLE 278 (general procedure (L))**

4-[1-(4-Cyclohexylphenyl)-3-(3-trifluoromethylsulfanylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

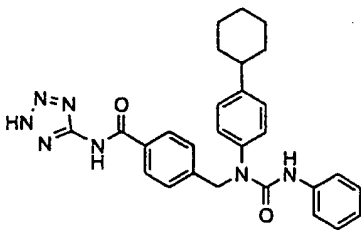
$^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  12.40 (s br, 1H); 8.58 (s, 1H); 8.05 (d, 2H); 7.90 (s, 1H); 7.70 (d, 1H); 7.45 (d, 2H); 7.40 (t, 1H); 7.30-7.15 (m, 5H); 5.00 (s, 2H); 1.85-1.10 (m, 11H).

HPLC-MS (method B):  $m/z$  = 596,  $R_t$  = 8.30 min.

10

**EXAMPLE 279 (general procedure (L))**

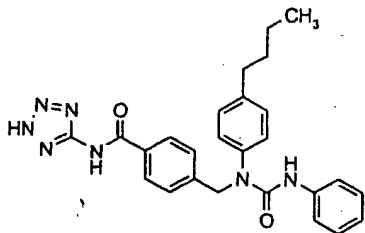
4-[1-(4-Cyclohexylphenyl)-3-phenylureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



15  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  12.35 (s br, 1H); 8.12 (s, 1H); 8.05 (d, 2H); 7.48 (d, 2H); 7.42 (t, 1H); 7.20 (m, 6H); 6.95 (t, 1H); 5.00 (s, 2H); 1.85-1.10 (m, 11H).

HPLC-MS (method B):  $m/z$  = 496,  $R_t$  = 7.72 min.

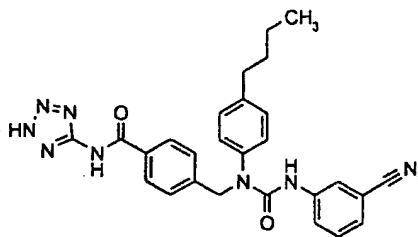


EXAMPLE 280 (general procedure (L))4-[1-(4-Butylphenyl)-3-phenylureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

- 5  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  12.35 (s br, 1H); 8.10 (s, 1H); 8.04 (d, 2H); 7.46 (d, 2H); 7.42 (d, 2H); 7.30-7.10 (m, 6H); 6.95 (t, 1H); 5.00 (s, 2H); 2.55 (t, 2H); 1.55 (k, 2H); 1.32 (sx, 2H); 0.90 (t, 3H).

HPLC-MS (method B):  $m/z$  = 470,  $R_t$  = 7.38 min.

10

EXAMPLE 281 (general procedure (L))4-[1-(4-Butylphenyl)-3-(3-cyanophenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

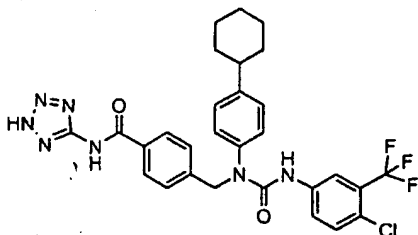
- 15  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  12.35 (s br, 1H); 8.50 (s, 1H); 8.05 (d, 2H); 7.95 (s, 1H); 7.75 (d, 1H); 7.46-7.38 (m, 4H); 7.20 (s, 4H); 5.00 (s, 2H); 2.55 (t, 2H); 1.55 (k, 2H); 1.32 (sx, 2H); 0.90 (t, 3H).

HPLC-MS (method B):  $m/z$  = 495,  $R_t$  = 7.28 min.

20

**EXAMPLE 282 (general procedure (L))**

4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 12.40 (s br, 1H); 8.70 (s, 1H); 8.05 (d+s, 3H); 7.80 (d, 1H); 7.55 (d, 1H); 7.45 (d, 2H); 7.22 (s, 4H); 5.00 (s, 2H); 1.85-1.10 (m, 11H).

HPLC-MS (method B):  $m/z$  = 598,  $R_t$  = 8.55 min.

10

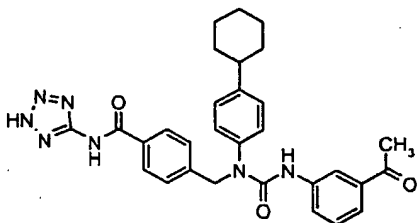
<sup>1</sup>H NMR (MeOH-*d*<sub>4</sub>): δ 1.20 – 1.50 (m, 5H), 1.75 – 1.90 (m, 5H), 2.55 (m, 1H), 5.02 (s, 2H), 7.19 (d, 2H), 7.30 (d, 2H), 7.44 – 7.50 (m, 3H), 7.60 (d, 1H), 7.90 (s, 1H), 7.99 (d, 2H).

MS (APCI, neg): 596.2, 597.2, 598.2, 375.2, 376.2.

15

### EXAMPLE 283 (general procedure (L))

4-[3-(3-Acetylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2*H*-tetrazol-5-yl)benzamide



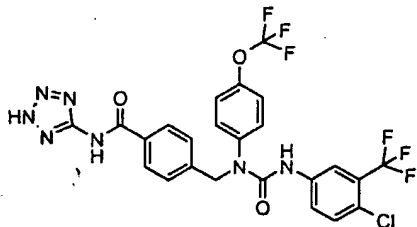
20 <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 12.40 (s br, 1H); 8.48 (s, 1H); 8.05 (d+s, 3H); 7.68 (d, 1H); 7.58 (d, 1H); 7.45 (d, 2H); 7.38 (t, 1H); 7.20 (s, 4H); 5.00 (s, 2H); 2.10 (s, 3H); 1.85-1.10 (m, 11H).

HPLC-MS (method B):  $m/z$  = 538,  $R_t$  = 7.38 min.

25

**EXAMPLE 284 (general procedure (L))**

**4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide**



5

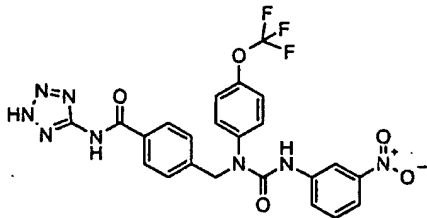
$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  12.40 (s br, 1H); 8.90 (s, 1H); 8.05 (d+s, 3H); 7.83 (d, 1H); 7.60 (d, 1H); 7.50-7.30 (m, 6H); 5.05 (s, 2H).

HPLC-MS (method B):  $m/z$  = 600,  $R_t$  = 7.75 min.

10

**EXAMPLE 285 (general procedure (L))**

**4-[3-(3-Nitrophenyl)-1-(4-trifluoromethoxyphenyl)ureidomethyl]ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide**

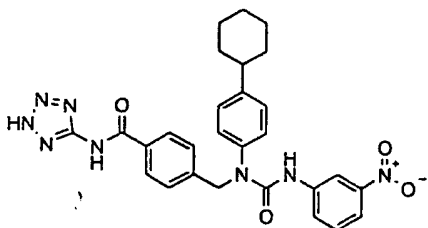


15

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  12.40 (s br, 1H); 9.00 (s, 1H); 8.48 (t, 1H); 8.05 (d, 2H); 7.92 (d, 1H); 7.82 (d, 1H); 7.60-7.30 (m, 7H); 5.05 (s, 2H).

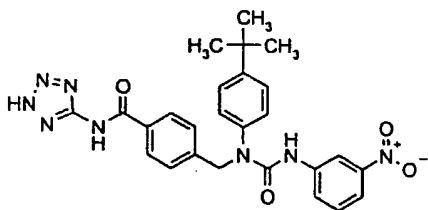
HPLC-MS (method B):  $m/z$  = 543,  $R_t$  = 6.62 min.

20

**EXAMPLE 286 (general procedure (L))****4-[1-(4-Cyclohexylphenyl)-3-(3-nitrophenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide**

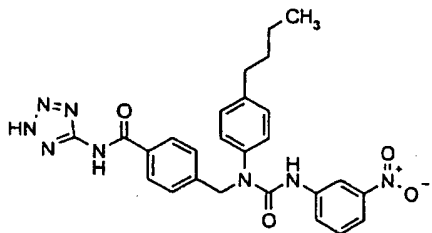
- 5  $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  12.40 (s br, 1H); 8.78 (s, 1H); 8.48 (t, 1H); 8.05 (d+s, 3H); 7.90 (d, 1H); 7.78 (d, 1H); 7.55-7.42 (m, 3H); 7.22 (s, 4H); 5.05 (s, 2H); 1.85-1.10 (m, 11H).

HPLC-MS (method B):  $m/z$  = 541,  $R_t$  = 7.67 min.

**10 EXAMPLE 287 (general procedure (L))****4-[1-(4-*tert*-Butylphenyl)-3-(3-nitrophenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide**

- $^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta$  12.40 (s br, 1H); 8.82 (s, 1H); 8.48 (t, 1H); 8.05 (d, 2H);  
15 7.93 (d, 1H); 7.81 (d, 1H); 7.60-7.35 (m, 5H); 7.25 (d, 2H); 5.05 (s, 2H); 1.30 (s, 9H).

HPLC-MS (method B):  $m/z$  = 515,  $R_t$  = 7.13 min.

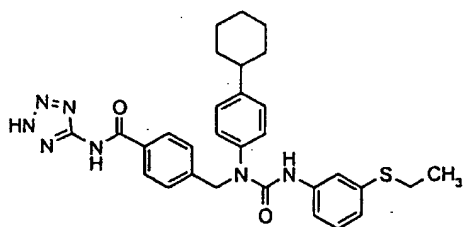
**EXAMPLE 288 (general procedure (L))****20 4-[1-(4-Butylphenyl)-3-(3-nitrophenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide**

$^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  12.40 (s br, 1H); 8.82 (s, 1H); 8.50 (t, 1H); 8.05 (d, 2H); 7.93 (d, 1H); 7.81 (d, 1H); 7.60-7.45 (m, 3H); 7.20 (s, 4H); 5.03 (s, 2H); 2.60 (t, 2H); 1.55 (k, 2H); 1.35 (sx, 2H); 0.90 (t, 3H).

5 HPLC-MS (method B):  $m/z$  = 515,  $R_t$  = 7.33 min.

EXAMPLE 289 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(3-ethylsulfanylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

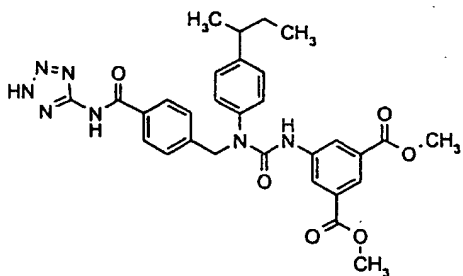


10

HPLC-MS (method B):  $m/z$  = 556,  $R_t$  = 8.07 min.

EXAMPLE 290 (general procedure (L))

15 5-[3-(4-sec-Butylphenyl)-3-[4-(2H-tetrazol-5-ylcarbonyl)benzyl]ureidoisophtalic acid dimethyl ester

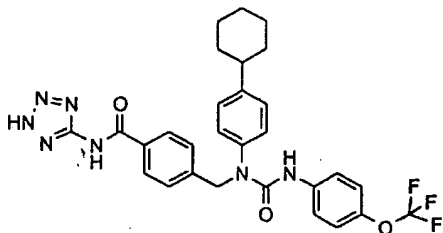


HPLC-MS (method B):  $m/z$  = 586,  $R_t$  = 7.23 min.

20

**EXAMPLE 291 (general procedure (L))**

4-[1-(4-Cyclohexylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



5

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.1-1.4 (5H, m), 1.65-1.85 (5H, m), 5.00 (2H, s), 7.2 (6H, m), 7.46 (2H, d), 7.55 (2H, d), 8.04 (2H, d), 8.43 (1H, s), 12.4 (1H, bs).

HPLC-MS (Method B):  $R_t$  = 8.22 min,  $m/z$  = 580 ( $M + 1$ ).

10

Alternative method for the preparation of the title compound:

To a solution of 4-carboxybenzaldehyde (40.2 g, 0.27 mol) in DMF (400 mL) was added *N*-ethyl-*N'*-3-dimethylaminopropylcarbodiimide (65.5 g, 0.33 mol) followed by 5-aminotetrazol monohydrate (36.6 g, 0.35 mol). The mixture was stirred for 24 hours at ambient temperature. The reaction volume was then reduced to one half by rotary evaporation, and water (800 mL) was added. The precipitate was collected by filtration, washed with cold acetonitrile and dried overnight in a vacuum oven to afford 46.0 g (80%) of 4-formyl-*N*-(2H-tetrazol-5-yl)benzamide.

15

20  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  8.08 (d, 2H); 8.26 (d, 2H); 10.15 (s, 1H); 12.68 (bs, 1H).

4-Formyl-*N*-(2H-tetrazol-5-yl)benzamide (8.94 g, 41.2 mmol) was dissolved in DMF (50 mL) by gentle heating. A solution of 4-cyclohexylaniline (7.20 g, 41.2 mmol) in methanol (100 mL) was added and a turbid suspension was formed. The suspension was heated to 70°C for 1 hour. Acetic acid (50 mL) and sodium cyanoborohydride (2.0 g, 31.7 mmol) was then added. The turbid suspension was heated to 70°C for an additional hour, before being cooled to 0°C on an ice bath. The insoluble material was collected by filtration and washed twice with water, before being dried overnight in a vacuum oven to afford 12.94 g (83.5%) of 4-[(4-cyclohexylphenylamino)methyl]-*N*-(2H-tetrazol-5-yl)benzamide.

25

30

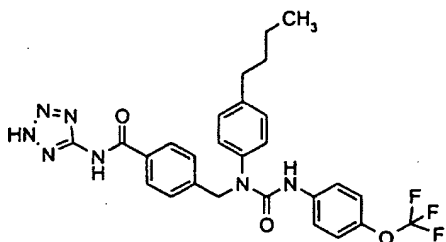
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.28 (m, 5H); 1.68 (m, 5H); 2.28 (m, 1H); 4.32 (s, 2H); 6.17 (bs, 1H); 6.48 (d, 2H); 6.88 (d, 2H); 7.52 (d, 2H); 8.03 (d, 2H); 12.30 (s, 1H).

To a suspension of 4-[(4-cyclohexylphenylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide  
5 (12.5 g, 33.2 mmol) in DMF (120 mL) was added 4-trifluoromethoxyphenyl isocyanate (6.8 g, 33.2 mmol). A clear solution was obtained upon heating to 80°C. After 30 minutes heating at 80°C, the solution was allowed to cool to room temperature. Solvent was removed by rotary evaporation, and the residual oil taken up into hot acetonitrile (500 mL). The title material, which separated out upon cooling, was collected by filtration and washed twice with cold ace-  
10 tonitrile to afford 15.32 g (80.0%) of the title compound.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.35 (m, 5H); 1.78 (m, 5H); 2.42 (m, 1H); 4.96 (s, 2H); 7.20 (s, 4H); 7.24 (d, 2H); 7.47 (d, 2H); 7.55 (d, 2H); 8.02 (d, 2H); 8.44 (s, 1H); 12.35 (s, 1H).

15 EXAMPLE 292 (general procedure (L))

4-[1-(4-Butylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide

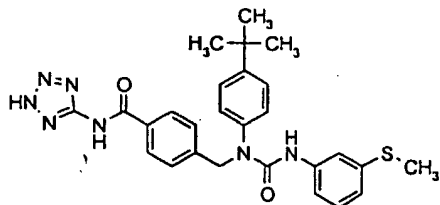


20 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.90 (3H, t), 1.33 (2H, sextet), 1.56 (2H, pentet), 2.55 (2H, partly hidden by DMSO), 5.00 (2H, s), 7.20 (4H, s), 7.23 (2H, d), 7.45 (2H, d), 7.57 (2H, d), 8.02 (2H, d), 8.36 (1H, s), 12.4 (1H, bs).

HPLC-MS (Method B): *R*<sub>t</sub> = 7.85 min, *m/z* = 554 (*M* + 1).

**EXAMPLE 293 (general procedure (L))**

4-[1-(4-*tert*-Butylphenyl)-3-(3-methylsulfanylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



5

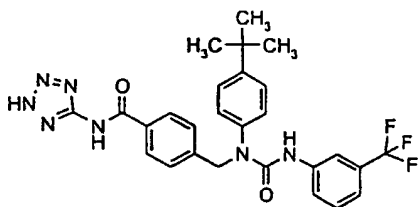
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.28 (9H, s), 2.43 (3H, s), 5.01 (2H, s), 6.36 (1H, d), 7.15 -7.25 (4H, m), 7.40 (3H, m), 7.48 (2H, d), 8.04 (2H, d), 8.25 (1H, s), 12.4 (1H, bs).

HPLC-MS (Method B):  $R_t$  = 7.42 min,  $m/z$  = 516 ( $M + 1$ ).

10

**EXAMPLE 294 (general procedure (L))**

4-[1-(4-*tert*-Butylphenyl)-3-(3-trifluoromethylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



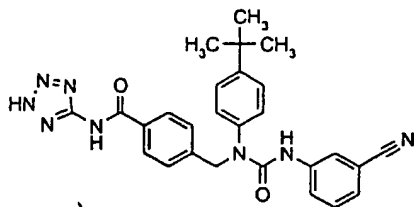
15

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.30 (9H, s), 5.01 (2H, s), 7.25 (2H, d), 7.30 (1H, d), 7.4-7.5 (5H, m), 7.75 (1H, m), 7.93 (1H, s), 8.05 (2H, d), 8.62 (1H, s), 12.4 (1H, bs).

HPLC-MS (Method B):  $R_t$  = 7.58 min,  $m/z$  = 538 ( $M + 1$ ).

20

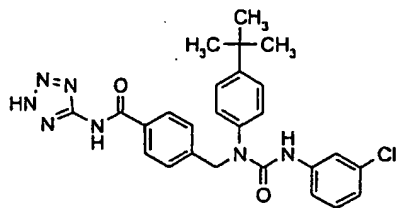


**EXAMPLE 295 (general procedure (L))****4-[1-(4-*tert*-Butylphenyl)-3-(3-cyanophenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide**

- 5  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.28 (9H, s), 5.00 (2H, s), 7.24 (2H, d), 7.4-7.5 (6H, m), 7.77 (1H, dt), 7.94 (1H, s), 7.93 (1H, s), 8.04 (2H, d), 8.60 (1H, s), 12.3 (1H, bs).

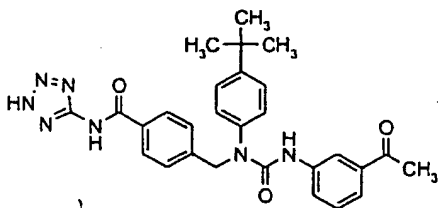
HPLC-MS (Method B):  $R_t$  = 6.83 min,  $m/z$  = 495 ( $M + 1$ ).

10 **EXAMPLE 296 (general procedure (L))**

**4-[1-(4-*tert*-Butylphenyl)-3-(3-chlorophenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide**

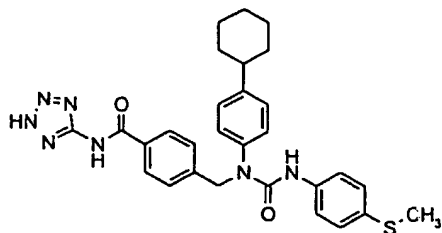
- 15  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.28 (9H, s), 5.01 (2H, s), 7.00 (1H, d), 7.2-7.25 (3H, m), 7.35-7.4 (3H, m), 7.47 (2H, d), 7.64 (1H, t), 8.05 (2H, d), 8.43 (1H, s), 12.4 (1H, bs).

HPLC-MS (Method C):  $R_t$  = 5.38 min,  $m/z$  = 504 ( $M + 1$ ).

EXAMPLE 297 (general procedure (L))4-[3-(3-Acetylphenyl)-1-(4-*tert*-butylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

- 5  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.28 (9H, s), 2.53 (3H, s), 5.03 (2H, s), 7.24 (2H, d), 7.4 (3H, m), 7.48 (2H, d), 7.57 (1H, d), 7.78 (1H, d), 8.0-8.05 (3H, m), 8.49 (1H, s), 12.4 (1H, bs).

HPLC-MS (Method C):  $R_t$  = 4.75 min,  $m/z$  = 512 ( $M + 1$ ).

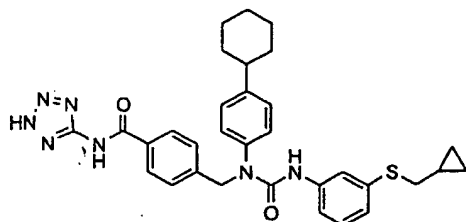
10 EXAMPLE 298 (general procedure (L))4-[1-(4-Cyclohexylphenyl)-3-(4-methylsulfanylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide

- 15  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.1-1.4 (5H, m), 1.6-1.8 (5H, m), 2.40 (3H, s), 5.00 (2H, s), 7.2 (6H, m), 7.40 (2H, d), 7.46 (2H, d), 8.04 (2H, d), 8.20 (1H, s), 8.0-8.05 (3H, m), 8.49 (1H, s), 12.3 (1H, bs).

HPLC-MS (Method C):  $R_t$  = 5.73 min,  $m/z$  = 542 ( $M + 1$ ).

EXAMPLE 299 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(3-cyclopropylmethylsulfanylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

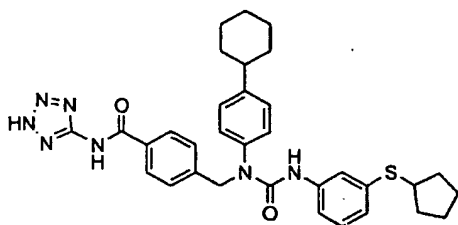


5

HPLC-MS (method B):  $m/z$ : 582,  $R_t$  = 8.28 min.

**EXAMPLE 300 (general procedure (L))**

4-[1-(4-Cyclohexylphenyl)-3-(3-cyclopentylsulfanylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

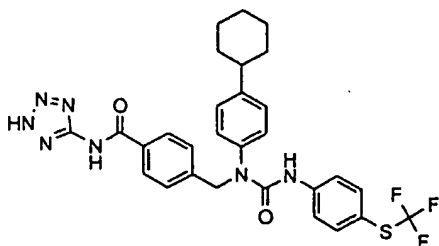


10

HPLC-MS (method B):  $m/z$ : 596,  $R_t$  = 8.70 min.

15 EXAMPLE 301 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(4-trifluoromethylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



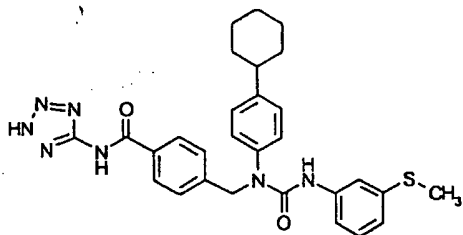
20

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.63 (s, 1H); 8.04 (d, 2H); 7.64 (d, 2H); 7.56 (d, 2H); 7.23 (d, 2H); 7.18 (d, 2H); 4.49 (s, 2H); 1.80 (m, 4H); 1.69 (m, 1H); 1.38 (m, 4H); 1.27 (m, 1H).

HPLC-MS (method B)  $m/z$  = 596,  $R_t$  = 8.58 min.

EXAMPLE 302 (general procedure (L))

- 5 4-[1-(4-Cyclohexylphenyl)-3-(3-methylsulfanylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

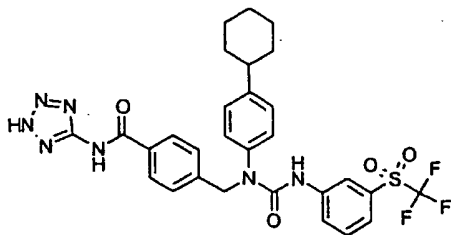


$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  8.22 (s, 1H), 7.95 (d, 2H), 7.40 (d, 3H), 7.25-7.10 (m, 6H), 6.83 (d, 1H), 4.97 (s, 2H), 4.02 (m, 1H), 2.42 (s, 3H), 1.85-1.15 (m, 10H).

HPLC-MS (method B):  $m/z$ : 542,  $R_t$  = 7.92 min.

EXAMPLE 303 (general procedure (L))

- 15 4-[1-(4-Cyclohexylphenyl)-3-(3-trifluoromethylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

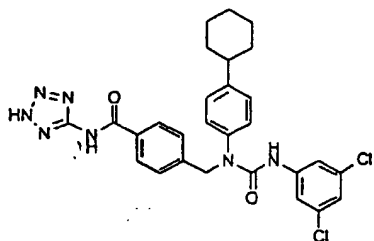


$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  12.4 (s, 1H), 8.90 (s, 1H), 8.32 (s, 1H), 8.11 (d, 1H), 8.03 (d, 2H), 7.70 (m, 2H), 7.45 (d, 2H), 7.23 (s, 4H), 5.00 (s, 2H), 1.85-1.15 (m, 10H).

HPLC-MS (method B):  $m/z$ : 628,  $R_t$  = 8.05 min.

EXAMPLE 304 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

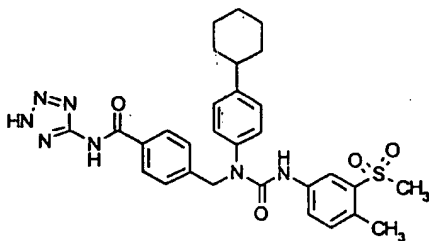
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  12.25 (s, 1H), 8.61 (s, 1H), 8.02 (d, 2H), 7.60 (s, 2H), 7.45 (d, 2H), 7.21 (dd, 4H), 7.15 (s, 1H), 4.97 (s, 2H), 1.85-1.15 (m, 10H).

HPLC-MS (method B):  $m/z$ : 564,  $R_t$  = 8.62 min.

10

EXAMPLE 305 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(3-methylsulfonyl-4-methylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



15

Preparation of intermediary 3-methylsulfonyl-4-methylaniline:

Under a nitrogen atmosphere, thionylchloride (4ml, 58 mmol) and methanesulphonic acid (9 mL, 146 mmol) were refluxed for 90 min. 4-Nitrotoluene (4 g, 29 mmol) and trifluoromethanesulphonic acid (200  $\mu\text{L}$ , 3 mmol) were added and the mixture was allowed to stand for 48 hours at 120°C. The mixture was cooled to 0°C and water (50 mL) was carefully added, followed by addition of ethyl acetate (150 mL). The organic phase was separated and extracted with a saturated solution of sodium hydrogencarbonate (2 x 50 mL) and water (2 x 50 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was purified by flash chromatography (heptane/ethylacetate, 1:1) to give 0.75 g of 2-methylsulfonyl-1-methyl-4-nitrobenzene.

25

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 2.78 (3H, s); 3.35 (3H, s); 7.78 (1H, d); 8.47(1H, dd); 8.63 (1H,s).

- 5 2-Methylsulfonyl-1-methyl-4-nitrobenzene (500 mg, 2.3 mmol) was dissolved in absolute ethanol (15 mL). Stannous chloride (2.6 g, 11.6 mmol) was added and the reaction mixture was stirred at 75°C for 4 hours. The mixture was poured into water (50 mL), pH was adjusted with a saturated solution of sodium carbonate to basic reaction, followed by addition of ethyl acetate (150 mL). The organic phase was extracted with water (2 x 50 mL), dried (MgSO<sub>4</sub>)  
10 and concentrated in vacuo to give 0.36 g of 3-methylsulfonyl-4-methylaniline as an oil.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 2.42 (3H, s); 3.11 (3H, s); 5.42 (2H, s); 6.75(1H, dd); 7.06 (1H, d); 7.16 (1H, d).

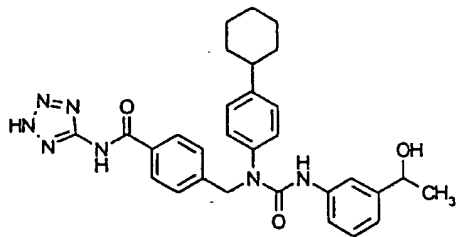
- 15 From 3-methylsulfonyl-4-methylaniline the corresponding isocyanato compound was prepared as described above. The isocyanato compound was used in step D of the general procedure (L) for the preparation of the title compound.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 12.35 (s, 1H), 8.05 (d, 2H), 7.52 (d, 2H), 7.39 (d, 2H), 6.49 (d, 1H),  
20 4.35 (s, 2H), 2.30 (m, 1H), 2.09 (s, 3H), 1.85-1.15 (m, 10H).

HPLC-MS (method B): m/z: 589, R<sub>t</sub> = 7.0 min.

EXAMPLE 306 (general procedure (L))

- 25 4-{1-(4-Cyclohexylphenyl)-3-[3-(1-hydroxyethyl)phenyl]ureidomethyl}-N-(2H-tetrazol-5-yl)benzamide



phase reduction of the 3-acetyl group using sodium borohydride in methanol as reducing agent.

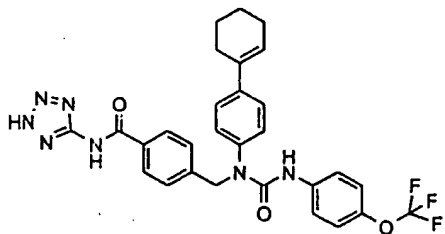
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 12.35 (s, 1H), 8.15 (s, 1H), 8.03 (d, 1H), 7.46 (d, 2H), 7.39 (s, 1H),  
5 7.32 (d, 1H), 7.20 (m, 5H), 6.90 (d, 1H), 5.10 (d, 1H), 5.00 (s, 2H), 4.63 (m, 1H), 1.85-1.15 (m, 13H).

HPLC-MS (method B): m/z: 540, R<sub>t</sub> = 6.9 min.

10 MA: calculated for C<sub>30</sub>H<sub>33</sub>N<sub>7</sub>O<sub>3</sub>:  
66.77% C, 6.16% H, 18.17% N; Found:  
66.52% C, 6.21% H, 17.93% N.

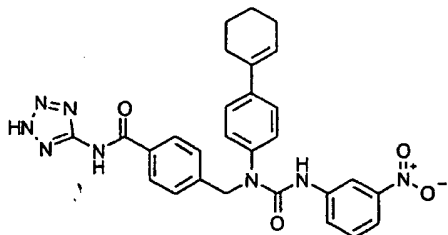
EXAMPLE 307 (general procedure (L))

15 4-[1-(4-Cyclohex-1-enylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.45 (s, 1H), 7.95 (d, 2H), 7.55 (d, 2H), 7.40 (dd, 4H), 7.20 (dd, 4H),  
20 6.18 (t, 1H), 5.00 (s, 2H), 2.35 (m, 2H), 2.18 (m, 2H), 1.72 (m, 2H), 1.60 (m, 2H).

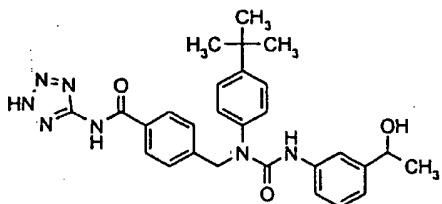
HPLC-MS (method B): m/z: 578, R<sub>t</sub> = 7.83 min.

**EXAMPLE 308 (general procedure (L))**4-[1-(4-Cyclohex-1-enylphenyl)-3-(3-nitrophenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

- 5 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.79 (s, 1H), 8.48 (s, 1H), 7.95 (m, 3H), 7.80 (d, 1H), 7.51 (t, 1H), 7.42 (dd, 4H), 7.22 (d, 2H), 6.19 (t, 1H), 5.00 (s, 2H), 2.35 (m, 2H), 2.18 (m, 2H), 1.72 (m, 2H), 1.60 (m, 2H).

HPLC-MS (method B): *m/z*: 539, *R*<sub>t</sub> = 7.3 min.

10

**EXAMPLE 309 (general procedure (L))**4-[1-(4-*tert*-Butylphenyl)-3-[3-(1-hydroxyethyl)phenyl]ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

15

The title compound was prepared using 3-acetylphenylisocyanate to give 4-[1-(4-*tert*-butylphenyl)-3-[3-acetylphenyl]ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide followed by solution phase reduction of the 3-acetyl group using sodium borohydride in methanol as reducing agent, before cleavage from the support.

20

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.18 (s, 1H), 8.03 (d, 2H), 7.48 (d, 2H), 7.39 (d, 2H), 7.32 (d, 1H), 7.20 (d, 2H), 7.15 (t, 1H), 6.90 (d, 1H), 5.10 (d, 1H), 5.00 (s, 2H), 4.63 (m, 1H), 1.3 (s, 9H).

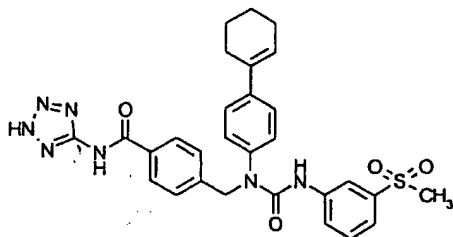
HPLC-MS (method B): *m/z*: 514, *R*<sub>t</sub> = 6.2 min.

25



EXAMPLE 310 (general procedure (L))

4-[1-(4-Cyclohex-1-enylphenyl)-3-(3-methylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

HPLC-MS (method B):  $m/z$ : 572,  $R_t$  = 6.4 min.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  12.3 (s, 1H), 9.08 (s, 1H), 8.25 (s, 2H), 8.03 (d, 2H), 7.61 (s, 1H), 7.42 (d, 2H), 7.11 (s, 1H), 4.65 (s, 2H), 4.08 (m, 1H), 1.80-0.75 (m, 9H), 0.81 (s, 9H)

10

HPLC-MS (method B):  $m/z$ : 612,  $R_t$  = 8.5 min.

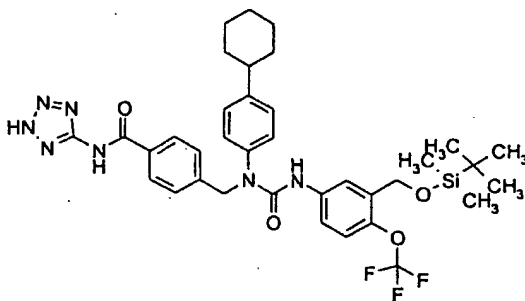
MA: calculated for  $\text{C}_{28}\text{H}_{31}\text{F}_6\text{N}_7\text{O}_2$ :

54.99% C; 5.11% H; 16.03% N; Found:

15 54.62% C; 5.15% H; 15.85% N.

EXAMPLE 311 (general procedure (L))

4-[3-[3-(*tert*-Butyldimethylsilanyloxymethyl)-4-trifluoromethoxyphenyl]-1-(4-cyclohexylphenyl)-ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



20

Fuming nitric acid (5 mL) was cooled on an ice bath. Methyl 2-(trifluoromethoxy)benzoate (5 g, 22.7 mmol) was slowly added within 30 minutes keeping the temperature below 15°C. The reaction was then stirred at 60°C for 1 hour and 2 hours at room temperature. The mixture

was poured on ice water whereupon an oil separated. The aqueous supernatant was decanted and additional water (50 mL) was added to the oil. After neutralisation with sodium hydrogen carbonate, the mixture was extracted with ethyl acetate (25 mL). The aqueous phase was extracted with ethyl acetate (15 mL) once more. The combined organic phases were washed with saturated sodium chloride (2 x 15 mL), dried ( $\text{MgSO}_4$ ), and concentrated in vacuo to give 5.69 g of 5-nitro-2-trifluoromethoxybenzoic acid methyl ester.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  3.93 (3H, s), 7.82 (1H, d), 8.58 (1H, d), 8.67 (1H, s)

10 HPLC-MS (method B):  $m/z$ : 266;  $R_t$  = 6.0 min.

5-Nitro-2-trifluoromethoxybenzoic acid methyl ester (5.69 g, 21.5 mmol) was dissolved in ethanol 99.9% (80 mL) and stannous (II) chloride dihydrate (24.2 g, 107 mmol) was added. The suspension was stirred on an oil-bath at  $75^\circ\text{C}$  for 2 hours and concentrated in vacuo.

15 Ethyl acetate (100 mL) and water (50 mL) was added and pH was adjusted to pH 8 with 4N sodium hydroxide (50 mL). The liquid was decanted from the precipitation. The precipitate was washed twice with ethyl acetate. The aqueous phase was extracted twice with ethyl acetate (60 mL). The combined organic phases were washed with a saturated sodium chloride solution (2 x 100 mL), dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. Purification by column chromatography (120 g silica) using ethyl acetate and heptane (1:1) as eluent afforded 3.8 g of 5-amino-2-trifluoromethoxybenzoic acid methyl ester.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  3.82 (3H, s), 5.63 (2H, s), 6.79 (1H, d), 7.07 (1H, s), 7.11 (1H, d)

25 HPLC-MS (method B):  $m/z$ : 236,  $R_t$  = 4.6 min.

5-Amino-2-trifluoromethoxybenzoic acid methyl ester (3.0 g, 12.8 mmol) was dissolved in THF (20 mL) in a three-necked flask equipped with a thermometer and an addition funnel under nitrogen. Under stirring and ice-cooling lithium aluminum hydride (1M in THF, 15 mL) was added dropwise within 10 minutes. Stirring was continued at room temperature for 1 hr, and the reaction was concentrated in vacuo. The residue was suspended in dichloromethane (150 mL) and water (50 mL), then filtered through celite, washed with dichloromethane and water. The filtrate was separated, and the water phase was extracted once more with dichloromethane (30 mL). The combined organic phases were washed with water (2 x 20 mL),

dried (MgSO<sub>4</sub>) and concentrated in vacuo to give 2.47 g of (5-amino-2-trifluoromethoxy-phenyl)methanol.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 3.92 (2H, d), 5.18 (1H, t), 5.28 (2H, s), 6.45 (1H, d), 6.91 (1H, d)

5

HPLC-MS (method B): m/z: 208, Rt = 7.2 min.

5-Amino-2-trifluoromethoxyphenyl)methanol (1.2 g, 5.8 mmol) was dissolved in DMF (5 mL) and imidazole (0.48 g, 7.1 mmol) and *tert*-butyldimethylsilyl chloride (0.99 g, 6.6 mmol) were added. The reaction mixture was stirred for 16 hours and water (20 mL) was added. The mixture was extracted with ethyl acetate (2 x 50 mL) and the combined organic phases were washed with water (10 mL), citric acid (10 mL, 10%) and water (2 x 10 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by column chromatography (110g, silica) using ethyl acetate and heptane (1:3) as eluent to give 1.2 g of 3-(*tert*-butyldimethylsilyloxymethyl)-4-trifluoromethoxyaniline.

15

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.82 (9H, s), 3.25 (6H, s), 4.52 (2H, s), 5.23 (2H, s), 6.41 (1H, d), 6.61 (1H, s), 6.86 (1H, d)

20 HPLC-MS (method B): m/z: 322; Rt = 7.17 min.

Triphosgene (0.09 g, 0.31 mmol) was dissolved in dichloromethane (2 mL) under nitrogen and cooled on ice. 3-(*tert*-Butyldimethylsilyloxymethyl)-4-trifluoromethoxyphenyl amine (0.3 g, 0.93 mmol) was evaporated twice with toluene and dissolved in dichloromethane (2 mL) and diisopropylethylamine (0.32 mL, 1.86 mmol) was added. This solution was then added to the solution of triphosgene, and after 2 hours at room temperature a slurry of 4-[(4-cyclohexylphenylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide (0.35 g, 0.93 mmol) in DMF (6 mL) was added. Before adding 4-[(4-cyclohexylphenylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide this was concentrated twice from toluene to remove any content of water. The mixture was stirred under nitrogen at 80°C for 2 hours and concentrated in vacuo, and the residue was extracted with dichloromethane (80 mL) and citric acid (25 mL, 10%). The aqueous phase was extracted with dichloromethane (30 mL) and the combined organic phases were washed with citrus acid (3 x 25 mL, 10%), dried and concentrated in vacuo. The residue was purified by column chromatography (35 g silica) using dichloromethane and 10% ammonia in

25

30

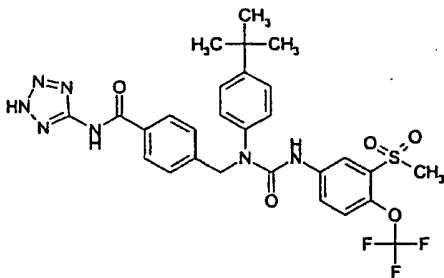
ethanol 85:15 as eluent to give 97 mg of 4-[3-[3-(*tert*-butyldimethylsilanyloxymethyl)-4-trifluoromethoxyphenyl]-1-(4-cyclohexylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.08 (6H, s), 0.89 (9H, s), 1.17-1.45 (5H, m), 1.67-1.82 (5H, m), 4.67  
5 (2H, s), 5.00 (2H, s), 7.16-7.25 (5H, m), 7.45 (3H, d), 7.63 (1H, s), 8.02 (2H, d), 8.44 (1H, s)  
11.97 (1H, broad).

HPLC-MS (method B): *m/z*: 610 (without dimethyl-*tert*-butylsilyl).

10 EXAMPLE 312 (general procedure (L))

4-[1-(4-*tert*-Butylphenyl)-3-(3-methylsulfonyl-4-trifluoromethoxyphenyl)ureidomethyl]-*N*-(2*H*-  
tetrazol-5-yl)benzamide



15 Synthesis of 3-methylsulfonyl-4-trifluoromethoxyphenyl isocyanate

To a solution of methyl iodide (59.0 g, 0.41 mol) in DMF (150 mL) was added potassium carbonate (23.0 g, 0.16 mol). 2-(Trifluoromethoxy)thiophenol (16.0 g, 0.08 mol) was added in portions during 30 minutes. The reaction mixture was then stirred vigorously overnight. Water (250 mL) was added. The reaction mixture was extracted with ethyl acetate (2 x 150 mL).

20 The combined organic phases were extracted with a 50% saturated aqueous solution of sodium chloride (4 x 100 mL), dried (MgSO<sub>4</sub>), and concentrated in vacuo to give 15.0 g of 1-methylsulfonyl-2-trifluoromethoxybenzene.

1-Methylsulfonyl-2-trifluoromethoxybenzene (15.0 g, 72 mmol) was dissolved in dichloromethane (200 mL) and *m*-chloroperoxybenzoic acid (39.0 g, 216 mmol) was added in small portions during 30 minutes. The reaction mixture was then allowed to stand overnight. Dichloromethane (200 mL) was added followed by slow addition of sodium hydroxide (2N, 200 mL). The organic phase was separated and extracted with sodium hydroxide (2N, 3 x 150 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo to give 15.8 g of 1-methylsulfonyl-2-trifluoromethoxybenzene.  
30

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.11 (d, 1H); 7.71 (t, 1H); 7.48 (m, 2H) 3.23(s 1H).

MA: Calculated for  $\text{C}_8\text{H}_7\text{F}_3\text{O}_3\text{S}$ :

- 5 40.00 % C, 2.94 % H; Found  
40.22 % C, 2.92 % H.

m.p. 44-46 °C.

- 10 1-Methylsulfonyl-2-trifluoromethoxybenzene (15.7 g, 65 mmol) was dissolved in concentrated  
sulfuric acid (27 mL) and the solution was heated to 40 °C. Nitric acid (100%, 27 mL) was  
added dropwise over 45 minutes. The reaction mixture was allowed to stand overnight at 60  
°C, cooled, and then poured on crushed ice (300 mL). The precipitated product was isolated  
by filtration, washed with water (10 x 50 mL) and dried ( $\text{MgSO}_4$ ), affording 17.5 g of 3-  
15 methylsulfonyl-4-trifluoromethoxynitrobenzene.

$^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.69 (d, 1H); 8.64 (d, 1H); 7.95 (d, 1H) 3.45 (s 3H).

MA: calculated for  $\text{C}_8\text{H}_6\text{F}_3\text{NO}_5\text{S}$ :

- 20 33.69% C, 2.12% H, 4.91% N; Found  
33.91% C, 2.08% H, 4.92% N.

m.p. 102-104 °C.

- 25 3-Methylsulfonyl-4-trifluoromethoxynitrobenzene (17.5g) was dissolved in methanol (400 mL)  
followed by addition of palladium on carbon (10%, 50% water, 3.2 g). The reaction mixture  
was hydrogenated for 17 hours at 1 atm of hydrogen, filtered and concentrated in vacuo to  
give 14.3 g of 3-methylsulfonyl-4-trifluoromethoxyaniline.

- 30  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.26 (d, 1H); 7.14 (d, 1H); 6.85 (dd, 1H) 5.89(s, 2H) 3.21(s,  
3H).

MA: calculated for  $\text{C}_8\text{H}_8\text{F}_3\text{NO}_3\text{S}$ :

- 35 37.65% C, 3.16% H, 5.49% N; Found,  
37.65% C, 3.14% H, 5.45% N.

m.p. 106-109 °C.

To 3-methylsulfonyl-4-trifluoromethoxyaniline (2.0 mmol, 500 mg) dissolved in ethyl acetate (6 ml) was added 3N HCl in ethyl acetate (5 ml) followed by concentration in vacuo. The residue was treated with toluene (3 x 5 mL) and each time concentrated in vacuo. To the residue was added toluene (10 mL) and trichloromethyl chloroformate (6 mmol, 0.73 mL), and under a N<sub>2</sub> atmosphere the suspension was gently refluxed for 2 hours at 120°C. Additional trichloromethyl chloroformate (6 mmol, 0.73 mL) was added and refluxing was continued overnight. The reaction mixture was concentrated in vacuo to afford 3-methylsulfonyl-4-trifluoromethoxyphenyl isocyanate.

Synthesis of 4-[1-(4-*tert*-butylphenyl)-3-(3-methylsulfonyl-4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

3-methylsulfonyl-4-trifluoromethoxyphenyl isocyanate was used without further characterisation for the preparation of the title compound.

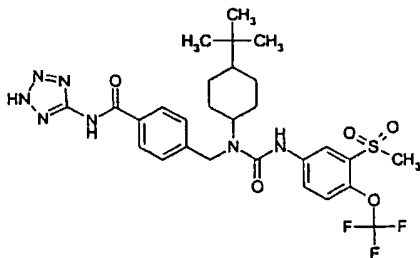
<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 10.72 (s, 1H); 10.38 (s, 1H); 8.51 (d, 1H); 8.28 (dd, 1H); 7.93 (d, 2H), 7.67 (dd 1H), 7.46 (d, 2H), 7.42 (d, 2H), 7.23 (d, 2H); 5.08 (s, 2H); 1.28 (s, 9H).

HPLC-MS (method B) m/z = 632, R<sub>t</sub> = 6.98 min.

The following examples were made similarly as described in example 312.

EXAMPLE 313 (general procedure (L))

4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-methylsulfonyl-4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



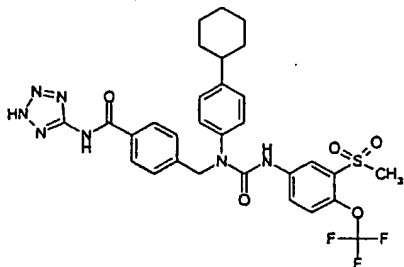
<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 12.25 (s, br, 1H); 8.95 (s, 1H); 8.19 (d, 1H), 8.04 (d 2H), 7.42 (d, 2H), 4.68 (s, 2H), 4.09 (t, br, 1H); 3.28 (s, 3H); 0.82 (s, 9H).

HPLC-MS (method B) *m/z* = 638, *R*<sub>t</sub> = 7.37 min.

5

EXAMPLE 314 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(3-methylsulfonyl-4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



10

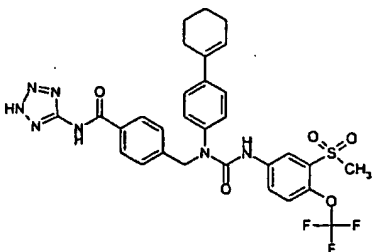
<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 10.72 (s, 1H); 10.38 (s, 1H); 8.51 (d, 1H), 8.28 (dd 1H), 7.93 (d, 2H), 7.67 (dd, 1H), 7.46 (d, 2H) 7.23 (s, 4H); 5.06 (s, 2H);

HPLC-MS (method B) *m/z* = 658, *R*<sub>t</sub> = 7.47 min.

15

EXAMPLE 315 (general procedure (L))

4-[1-(4-Cyclohex-1-enylphenyl)-3-(3-methylsulfonyl-4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



20

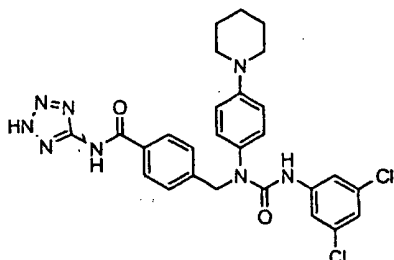
<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 10.72 (s, 1H); 10.46 (s, 1H), 8.52 (d, 1H); 8.28 (dd, 1H), 7.93 (d, 2H), 7.46 (d, 2H), 7.41 (d, 2H), 7.23 (d, 2H), 6.18 (s, 1H), 3.27 (m, 2H), 2.18 (m, 2H), 1.71 (m, 2H), 1.6 (m, 2H)

HPLC-MS (method B) *m/z* = 656, *R*<sub>t</sub> = 7.23 min.

25

EXAMPLE 316 (general procedure (L))

4-[3-(3,5-Dichlorophenyl)-1-(4-piperidin-1-ylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



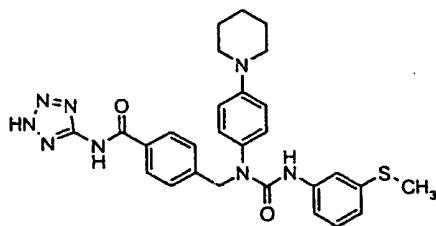
5

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  4.90 (2H, s), 6.91 (2H, d), 7.07 (2H, d), 7.13 (1H, t), 7.44 (2H, d), 7.65 (2H, d), 8.02 (2H, d), 8.28 (1H, s).

10 HPLC-MS (Method B):  $m/z$  = 565 (M+1),  $R_t$  = 4.37 min.

EXAMPLE 317 (general procedure (L))

4-[3-(3-Methylsulfanyphenyl)-1-(4-piperidin-1-ylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



15

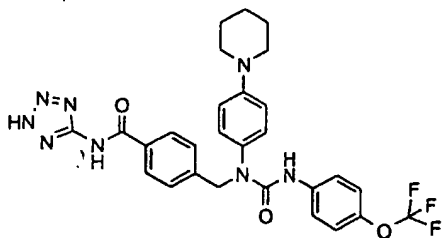
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  4.97 (2H, s), 6.83 (1H, d), 6.95-7.25 (6H, m), 7.4-7.5 (3H, m), 7.95 (1H, s), 8.00 (2H, d), 12.4 (1H, s).

20 HPLC-MS (Method B):  $m/z$  = 543 (M+1),  $R_t$  = 4.72 min.



EXAMPLE 318 (general procedure (L))

4-[1-(4-Piperidin-1-ylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



5

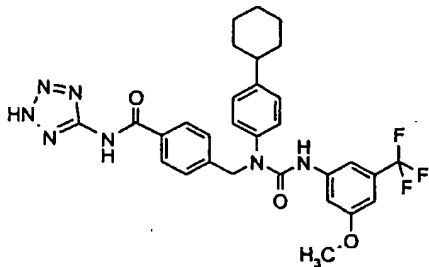
$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.5-1.6 (6H, m), 3.15 (4H, bs), 4.93 (2H, s), 6.94 (2H, d), 7.10 (2H, d), 7.22 (2H, d), 7.45 (2H, d), 7.55 (2H, d), 8.03 (2H, d), 8.10 (1H, s), 12.4 (1H, s).

HPLC-MS (Method B):  $m/z$  = 581 ( $M+1$ ),  $R_t$  = 5.02 min.

10

EXAMPLE 319 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(3-methoxy-5-trifluoromethylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



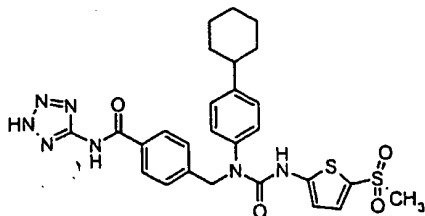
15

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  12.40 (br s, 1H); 8.60 (s, 1H); 8.05 (d, 2H); 7.52 (s, 1H); 7.48 (s, 1H); 7.46 (d, 2H); 7.20 (dd, 4H); 6.80 (s, 1H); 5.03 (s, 2H); 3.78 (s, 3H); 1.85-1.60 (m, 5H); 1.50-1.15 (m, 5H).

20 HPLC-MS (Method B):  $m/z$  = 594 ( $M+1$ ).  $R_t$  = 7.92 min.

EXAMPLE 320 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(5-methylsulfonylthiophen-2-yl)-ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

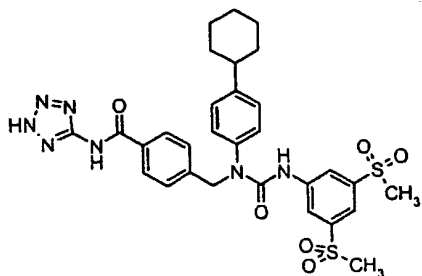


$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  12.40 (s, 1H); 10.10 (s, 1H); 8.06 (d, 2H); 7.42 (m, 3H); 7.28 (d, 2H); 7.19 (d, 2H); 6.70 (d, 1H); 3.20 (s, 3H); 1.75-1.60 (m, 5H); 1.50-1.10 (m, 5H).

HPLC-MS (Method B):  $m/z$  = 580 (M+1).  $R_t$  = 6.45 min.

EXAMPLE 321 (general procedure (L))

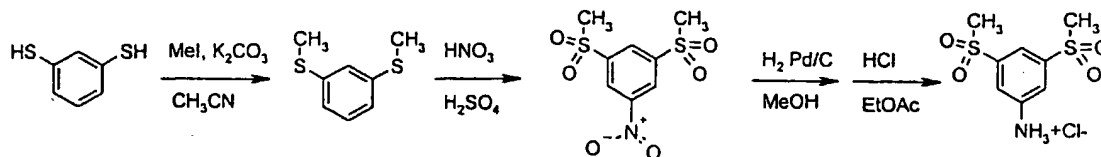
4-[3-(3,5-Bis(methylsulfonyl)phenyl)-1-(4-cyclohexylphenyl)-ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  8.45 (s, 2H); 8.05-7.95 (m, 3H); 7.50-7.42 (m, 2H); 7.22 (dd, 4H); 5.00 (s, 2H); 1.90-1.70 (m, 5H); 1.45-1.30 (m, 5H).

HPLC-MS (Method B):  $m/z$  = 652 (M+1).  $R_t$  = 6.33 min.

Preparation of 3,5-bis(methylsulfonyl)phenylamine:



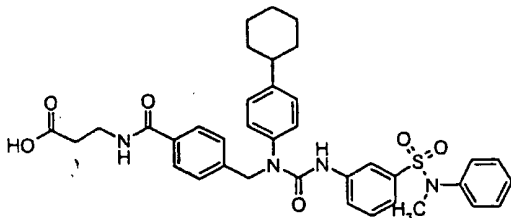
1,3-Bis-benzenethiol (5 g, 35.2 mmol) was dissolved in acetonitrile (50 mL) and added iodo-  
methane (4.62 mL, 73.9 mmol) and potassium carbonate (10.7 g, 77.4 mmol). Upon stirring  
5 overnight at 25°C, the mixture was filtered and the solvent removed in vacuo. The residue  
was partitioned between water (100 mL) and ethyl acetate (100 mL). The aqueous layer was  
extracted with ethyl acetate (2 x 50 mL) and the combined organic extracts were dried with  
MgSO<sub>4</sub> and evaporated. The residue was distilled at 17 torr, 138°C affording 1,3-  
bis(methylsulfonyl)benzene (3.20 g).

The above 1,3-bis(methylsulfonyl)benzene (3.20 g) was dissolved in H<sub>2</sub>SO<sub>4</sub> (8 mL) and  
cooled on an ice bath. A mixture of H<sub>2</sub>SO<sub>4</sub> and HNO<sub>3</sub> (1:1, 10 mL) was added dropwise.  
Upon stirring 30 min at 25°C, the temperature was raised to 100°C and kept there for 3  
hours. Pouring the reaction mixture onto ice (100 mL) afforded a precipitate that still con-  
15 tained starting material (2.90 g). This material was dissolved in H<sub>2</sub>SO<sub>4</sub> (5.2 mL) and added a  
mixture of H<sub>2</sub>SO<sub>4</sub> and HNO<sub>3</sub> (1:1, 10.4 mL). The mixture was heated at 110°C overnight and  
poured onto ice (100 mL). The formed precipitate was collected by filtration (1.01 g). Chro-  
matography on silica gel using a mixture of heptane and ethyl acetate (4:1) as eluent af-  
forded the desired 1,3-bis(methylsulfonyl)-5-nitrobenzene (0.7 g).

To a slurry of 1,3-bis(methylsulfonyl)-5-nitrobenzene (0.7 g) in methanol (10 mL) was added  
palladium on charcoal (0.1 g) and the mixture was hydrogenated at atmospheric pressure  
and 25°C for 1 hour. The reaction mixture was filtered and evaporated. The residue was sus-  
pended in ethyl acetate (25 mL) and HCl in ethyl acetate (5 mL, appr. 2M) was added. Filtra-  
25 tion afforded the desired aniline as its hydrochloride salt, which was converted into an isocy-  
anate using diphosgene as described previously.

EXAMPLE 322 (general procedure (L))

3-(4-{1-(4-Cyclohexylphenyl)-3-[3-(methylphenylsulfamoyl)phenyl]ureidomethyl}-benzoyl-amino)propionic acid

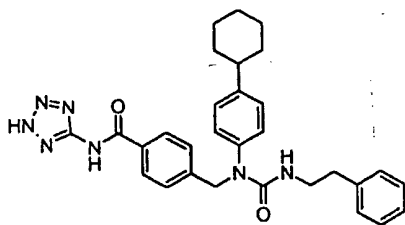


5

HPLC-MS (Method B):  $m/z$  = 669 ( $M+1$ ).  $R_t$  = 7.38 min.

EXAMPLE 323 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-phenethylureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



10

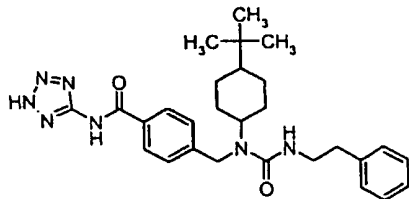
$^1\text{H}$  NMR (DMSO):  $\delta$  12.40 (s, 1H); 8.00 (d, 2H); 7.40-7.08 (m, 8H); 7.02 (d, 2H); 5.70 (t, 1H); 4.90 (s, 2H); 3.27 (q, 2H); 2.72 (t, 2H); 1.75-1.62 (m, 5H); 1.45-1.10 (m, 5H)

HPLC-MS (Method B):  $m/z$  = 524 ( $M+1$ ).  $R_t$  = 7.35 min.

15

EXAMPLE 324 (general procedure (L))

4-[1-(4-tert-Butylcyclohexyl)-3-phenethylureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



20

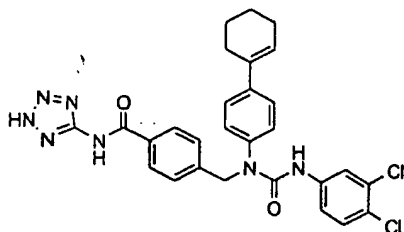
$^1\text{H}$  NMR (DMSO):  $\delta$  12.35 (s, 1H); 8.00 (d, 2H); 7.45-7.10 (m, 7H); 6.45 (s br 1H); 4.50 (d br 2H); 4.10+3.85 (s br, 1H); 3.30 (s br, 2H); 2.80 (s br, 2H); 1.80-1.00 (m, 9H); 0.80 (s, 9H).

HPLC-MS (Method B):  $m/z$  = 504 ( $M+1$ ).  $R_t$  = 7.05 min.

EXAMPLE 325 (general procedure (L))

4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,4-dichlorophenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-

5 benzamide

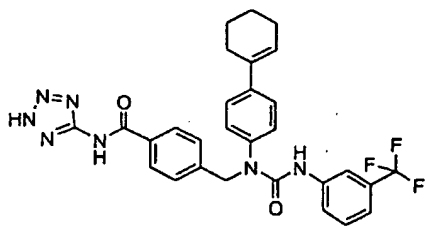


$^1\text{H}$  NMR (DMSO):  $\delta$  12.30 (s, 1H); 8.52 (s, 1H); 8.05 (d, 2H); 7.70 (s, 1H); 7.50-7.38 (m, 6H); 7.20 (d, 2H); 6.18 (s br, 1H); 5.00 (s, 2H); 2.38 (m, 2H); 2.15 (m, 2H); 1.71 (m, 2H); 1.58 (m, 2H).

HPLC-MS (Method B):  $m/z$  = 562 ( $M+1$ ).  $R_t$  = 7.90 min.

EXAMPLE 326 (general procedure (L))

15 4-[1-(4-Cyclohex-1-enylphenyl)-3-(3-trifluoromethylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-  
benzamide

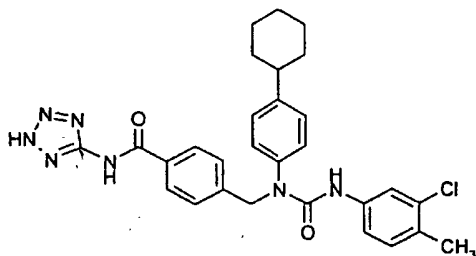


$^1\text{H}$  NMR (DMSO):  $\delta$  12.35 (s, 1H); 8.60 (s, 1H); 8.05 (2H); 7.91 (s, 1H); 7.78 (d, 1H); 7.48-7.40 (m, 5H); 7.30 (d, 1H); 7.23 (d, 2H); 6.20 (t, 1H); 5.00 (s, 1H); 2.38 (m, 2H); 2.15 (m, 2H); 1.72 (m, 2H); 1.60 (m, 2H).

HPLC-MS (Method B):  $m/z$  = 562 ( $M+1$ ).  $R_t$  = 7.73 min.

**EXAMPLE 327 (general procedure (L))**

4-[3-(3-Chloro-4-methylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



5

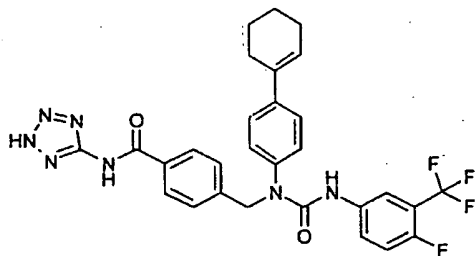
HPLC-MS (method B): m/z: 544,  $R_t$  = 7.88 min.

$^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ):  $\delta$  1.18-1.48 (5H, m), 1.66-1.87 (5H, m), 2.26 (3H, s), 5.00 (2H, s), 7.22 (4H, dd), 7.3 (2H, d), 7.47 (2H, d), 7.62 (1H, s), 8.02 (2H, d), 8.30 (1H, s), 12.2 (1H, broad).

10

**EXAMPLE 328 (general procedure (L))**

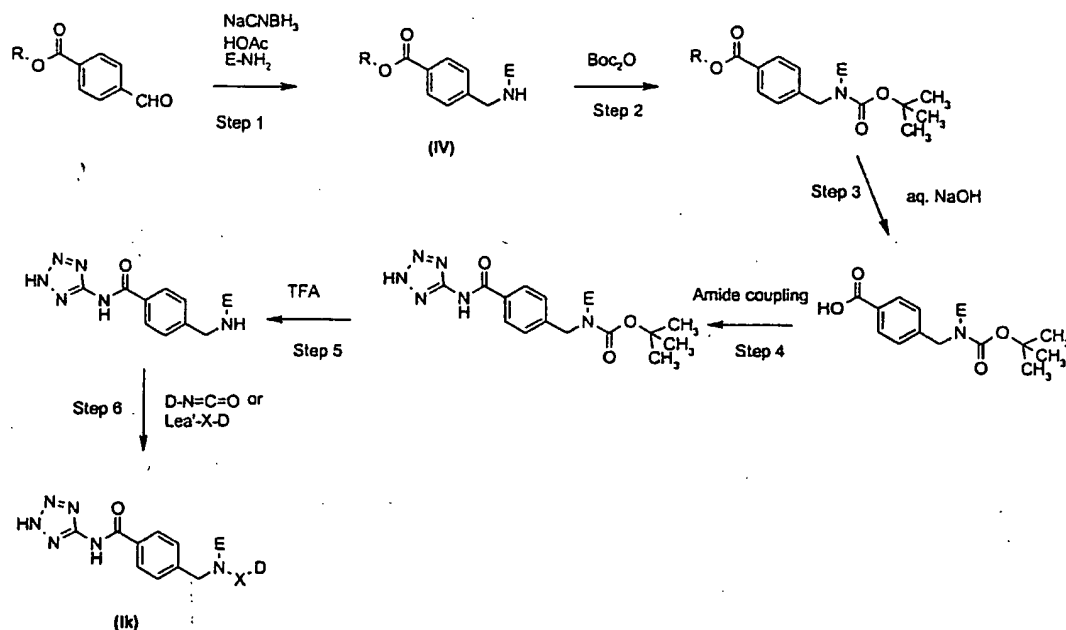
4-[1-(4-Cyclohex-1-enylphenyl)-3-(4-fluoro-3-trifluoromethylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



15

HPLC-MS (method B): m/z: 580,  $R_t$  = 7.67 min.

General procedure (M) for the solution phase synthesis of compounds of general formula (Ik):



5

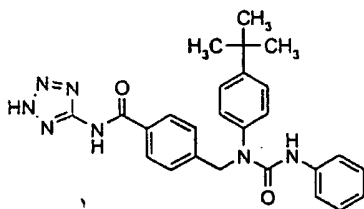
wherein R is  $C_{1-6}$ -alkyl,

X, D, and E are as defined in general formula (I), and

10 Lea' is a leaving group such as -OSu, chloro, phenoxy, or 4-nitrophenoxy.

In case the intermediate of the formula (IV) is a mixture of isomers, separation of these can either be performed by column chromatography of the intermediate of the formula (IV) or crystallisation of the intermediate imine.

15

EXAMPLE 329 (general procedure (M))4-[1-(4-*tert*-Butylphenyl)-3-phenylureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamideStep 1:

Step 1 is the same as described in general procedure (K). Alternatively, it can be performed as described for step A of the general procedure (F).

Step 2:

- 4-[(4-*tert*-Butylphenylamino)methyl]benzoic acid methyl ester (18.3 g, 61 mmol, prepared as described above) was dissolved in THF (300 mL) and *N,N*-diisopropylethylamine (15 mL, 3.13 mmol), a catalytic amount of 4-dimethylaminopyridine, and di-*tert*-butyldicarbonate (14.8 g, 68 mmol) was added. The resulting mixture was refluxed for 16 hours, cooled and concentrated in vacuo.

Step 3:

- The residue was dissolved in ethanol (450 mL) and added 4N aqueous sodium hydroxide (135 mL) and the mixture was stirred at room temperature for 3 days. 4N Hydrochloric acid (140 mL) was added with occasional cooling by addition of crushed ice. The mixture was filtered and the solid was washed with water and dried in vacuo at 30°C to afford 14.5 g (62%) of 4-[(*tert*-butoxycarbonyl-(4-*tert*-butylphenyl)amino)methyl]benzoic acid as a solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.29 (9H, s), 1.42 (9H, s), 4.89 (2H, s), 7.10 (2H, bd), 7.28 (2H, d), 7.37 (2H, d), 8.05 (2H, d).

HPLC-MS (Method B): R<sub>t</sub> = 8.10 min, m/z = 328 ((M-<sup>t</sup>Bu)+1) (trace: 384 (M+1)).

Step 4:

- The above benzoic acid (2.80 g, 7.3 mmol) was dissolved in DMF (20 mL) and 1-hydroxy-benzotriazol (1.18 g, 8.8 mmol) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (1.54 g, 8.0 mmol) were added and the resulting mixture was stirred at room tem-



perature for 1 hour. 5-Aminotetrazole hydrate (0.90 g, 8.8 mmol) was added and the mixture was stirred at room temperature for 16 hours. Water (75 mL) was added and the mixture was extracted with ethyl acetate (2 x 75 mL). The combined organic phases were washed with a mixture of water and saturated aqueous sodium chloride (1:1, 2 x 100 mL) and water (100 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was crystallised from diethyl ether (30 mL) to afford 1.89 g (57%) of (4-*tert*-butylphenyl)-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]carbamic acid *tert*-butyl ester as a solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.29 (9H, s), 1.43 (9H, s), 4.93 (2H, s), 7.13 (2H, bd), 7.30 (2H, d), 8.28 (2H, d), 12.5 (1H, s).

HPLC-MS (Method B): R<sub>t</sub> = 7.63 min, m/z = 395 ((M-<sup>t</sup>Bu)+1) (trace: 451 (M+1)).

Step 5:

The above carbamic acid *tert*-butyl ester (1.7 g, 3.77 mmol) was suspended in ethyl acetate (12 mL) and a 3.4 M dry HCl solution in ethyl acetate (12 mL) was added and the suspension was stirred at room temperature for 16 hours. The mixture was concentrated in vacuo and re-suspended in ethyl acetate. Concentration in vacuo afforded 1.49 g (100%) of 4-[(4-*tert*-butylphenylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide hydrochloride as a solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.37 (9H, s), 4.56 (2H, s), 7.18 (2H, bd), 7.38 (2H, d), 7.68 (2H, d), 8.19 (2H, d), 12.4 (1H, s).

HPLC-MS (Method B): R<sub>t</sub> = 5.22 min, m/z = 351 (M + 1).

Step 6:

The above benzamide hydrochloride (242 mg, 0.63 mmol) was mixed with dichloromethane (10 mL), *N,N*-diisopropylethylamine (330 μL, 1.89 mmol), and phenylisocyanate (68 μL, 0.63 mmol) and the resulting mixture was stirred at 25°C for 16 hours. Alternatively, Lea'-X-D can be used in which case a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any tertiary amine or potassium carbonate has to be added. The mixture was diluted with dichloromethane (20 mL) and the mixture was washed with saturated aqueous citric acid (20 mL), the organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was crystallised from diethyl ether to afford 141 mg (48%) of the title compound as a solid.

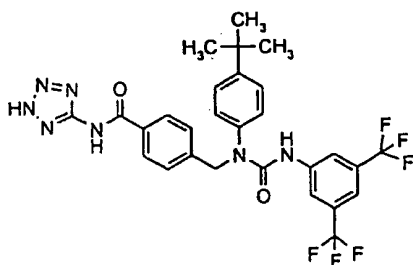
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.29 (9H, s), 5.00 (2H, s), 6.95 (1H, t), 7.2-7.3 (4H, m), 7.3-7.5 (7H, m), 8.04 (2H, d), 8.18 (1H, s), 12.3 (1H, s).

5 HPLC-MS (Method B): R<sub>t</sub> = 7.22 min, m/z = 470 (M +1).

Similarly, the following compounds were made.

EXAMPLE 330 (general procedure (M))

10 4-[3-(3,5-Bis(trifluoromethyl)phenyl)-1-(4-*tert*-butylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

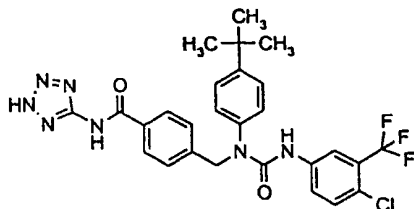


<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.29 (9H, s), 5.01 (2H, s), 7.30 (1H, t), 7.43 (2H, d), 7.47 (2H, d), 7.64 (1H, s), 8.05 (2H, d), 8.25 (2H, s), 9.00 (1H, s) 12.3 (1H, s).

HPLC-MS (Method B): R<sub>t</sub> = 8.43 min, m/z = 606 (M +1).

EXAMPLE 331 (general procedure (M))

20 4-[1-(4-*tert*-Butylphenyl)-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

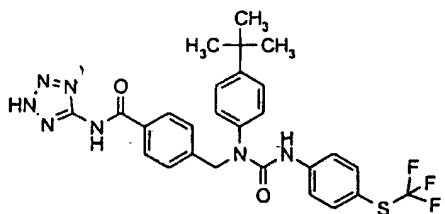


<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.28 (9H, s), 5.01 (2H, s), 7.23 (2H, d), 7.40 (2H, d), 7.45 (2H, d), 7.56 (1H, d), 7.80 (1H, dd), 8.05 (3H, m), 8.73 (1H, s) 12.3 (1H, s).

HPLC-MS (Method B):  $R_t = 8.18$  min,  $m/z = 572$  ( $M + 1$ ).

**EXAMPLE 332 (general procedure (M))**

4-[1-(4-*tert*-Butylphenyl)-3-(4-trifluoromethylsulfonylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

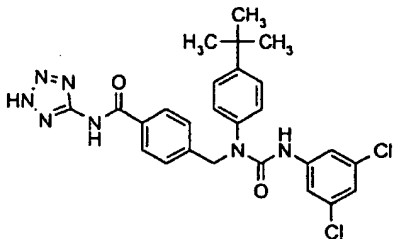


$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.28 (9H, s), 5.02 (2H, s), 7.21 (2H, d), 7.38 (2H, d), 7.46 (2H, d), 7.56 (2H, d), 7.63 (2H, d), 8.04 (2H, d), 8.64 (1H, s) 12.3 (1H, s).

HPLC-MS (Method B):  $R_t = 8.20$  min,  $m/z = 570$  ( $M + 1$ ).

**EXAMPLE 333 (general procedure (M))**

4-[1-(4-*tert*-Butylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

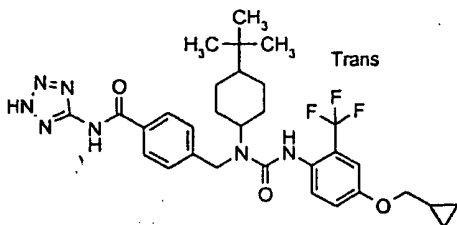


$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.35 (9H, s), 4.95 (2H, s), 6.88 (1H, s), 6.96 (1H, t), 7.10 (2H, d), 7.38 (2H, d), 7.43 (4H, m), 8.13 (2H, d), 8.64 (1H, s) 12.3 (1H, s).

HPLC-MS (Method B):  $R_t = 7.98$  min,  $m/z = 538$  ( $M + 1$ ).

**EXAMPLE 334 (general procedure (M))**

**4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-cyclopropylmethoxy-2-trifluoromethylphenyl)ureido-methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide**



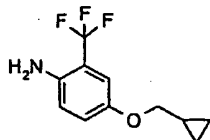
5

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 7.98 (3H, m), 7.42 (2H, d), 7.32 (1H, d), 7.18 (1H, d), 7.13 (1H, s), 4.55 (2H, broad), 3.88 (2H, d), 1.80-0.85 (10H, m), 0.80 (9H, s), 0.60 (2H, m), 0.33 (2H, m).

HPLC-MS (method B): *m/z*: 614, *R*<sub>t</sub> = 8.32 min.

10

Synthesis of intermediate 4-cyclopropylmethoxy-2-trifluoromethylphenylamine:



1-Nitro-4-hydroxy-2-trifluoromethylbenzene (5.0 g, 14 mmol) and cyclopropylcarbinol (1.75 g, 24 mmol) were dissolved in THF (20 mL) under nitrogen. Triphenylphosphine (9.5 g, 36 mmol) was added and diethyl azodicarboxylate (5.7 mL, 36 mmol) dissolved in THF (10 mL) was added over 30 minutes. The reaction mixture was stirred at 20°C for 16 hours and then concentrated in vacuo. The residue was dissolved in ethyl acetate (25 mL) and heptane (40 mL). The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (350 g silica) using heptane and ethyl acetate (9:1) as eluent to give 1.4 g of 4-cyclopropylmethoxy-1-nitro-2-trifluoromethylbenzene.

20

HPLC-MS (method B): *m/z*: 262, *R*<sub>t</sub> = 7.6 min.

25

Stannous chloride (4.75 g, 21 mmol) was added to a solution of 4-cyclopropylmethoxy-1-nitro-2-trifluoromethylbenzene (1.1 g, 4.2 mmol) in ethanol (12 mL). The reaction temperature was raised to 70°C for 1.5 hour. The reaction mixture was concentrated in vacuo and the residue dissolved in ethyl acetate (20 mL). Water (15 mL) was added and sodium hydrogen

carbonate was added until pH 7. The mixture was filtered and the organic phase collected. The aqueous phase was extracted with ethyl acetate (20 mL). The combined organic phases were dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was purified by flash chromatography (38 g) using heptane and ethyl acetate (9:1) as eluent to give 0.49 g of 4-cyclopropylmethoxy-2-trifluoromethylphenylamine.

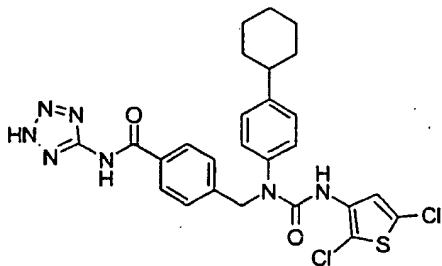
$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  6.98 (1H, d), 6.85 (1H, s), 6.79 (1H, d), 5.10 (2H, broad), 3.72 (2H, d), 1.15 (1H, m), 0.53 (2H, m), 0.31 (2H, m).

HPLC-MS (method B):  $m/z$ : 232,  $R_t$  = 5.9 min.

This intermediate product was transformed to the corresponding phenylcarbamate using the same methodology as described in example 239 and used for the synthesis of the title compound.

EXAMPLE 335 (general procedure (M))

4-[1-(4-Cyclohexylphenyl)-3-(2,5-dichlorothiophen-3-yl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



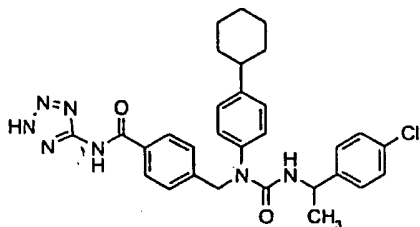
The intermediate 2,5-dichloro-3-thienylisocyanate was prepared by a Curtius reaction on 2,5-dichloro-3-thienylcarboxylic acid.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  7.63 (s, 1H), 7.49 (d, 2H), 7.33 (d, 2H), 7.27 (s, 1H), 7.22 (dd, 4H), 4.88 (s, 2H), 1.8-1.6 (m, 5H), 1.4-1.2 (m, 6H)

HPLC-MS (method B):  $m/z$ : 567,  $R_t$  = 8.5 min.

**EXAMPLE 336 (general procedure (M))**

4-[3-[1-(4-Chlorophenyl)ethyl]-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



5

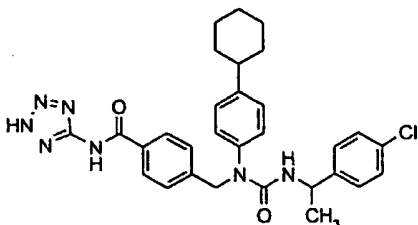
HPLC-MS (Method B):  $m/z$  = 558 ( $M+1$ ),  $R_t$  = 7.83 min.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.2 – 1.4 (8H, m), 1.7 – 1.8 (5H, m), 4.90 (3H, m), 7.1 – 7.2 (4H, m), 7.35 (5H, m), 7.52 (1H, m), 8.02 (2H, d).

10

**EXAMPLE 337 (general procedure (M))**

4-[3-[1-(4-Chlorophenyl)ethyl]-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide, enantiomer A, first eluted



15

The compound of example 336 was separated into pure enantiomers using a (*R,R*)-Whelk-O 1 column (250-21.1 mm, Regis) eluted with *n*-heptane:ethanol, 1:1 at a flow rate of 15 mL/min. The compound was dissolved in ethyl acetate:ethanol:acetic acid:*n*-heptane (0.9:1.1:0.09:1.1), 5 mg/ml, injected in portions of 10  $\mu\text{g}$  (2  $\mu\text{l}$ ) and detected at 225 and 254 nm. The two enantiomers A and B eluted at  $T_R$  9-12 min (A) and  $T_R$  37-42 min (B), respectively, and the fractions were collected (10 mL/fraction) and pooled. The purity of the enantiomers was determined using a Chiralcel OD (250-4.6mm, Daicel) column eluted with ethanol:(*n*-heptane+0.1% TFA), 40:60 at a flow rate of 0.6 mL/min,  $T_R$ (A): 14.6 min and  $T_R$ (B): 12.0 min.

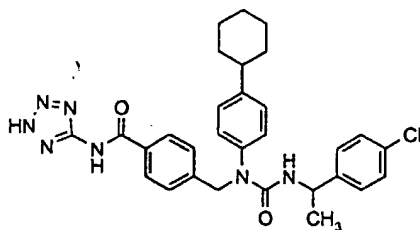
25

Used instruments:

HP1090 (analytical runs), Gilson HPLC system (preparative runs).

EXAMPLE 338 (general procedure (M))

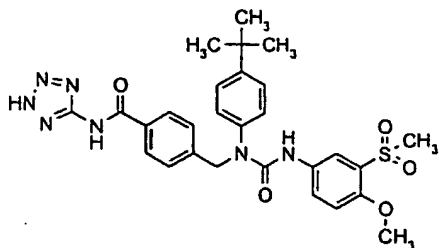
4-[3-[1-(4-Chlorophenyl)ethyl]-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide, enantiomer B, second eluted



This compound was obtained as the second eluting enantiomer (enantiomer B) of example 337. For HPLC-data, see example 337.

EXAMPLE 339 (general procedure (M))

4-[1-(4-tert-Butylphenyl)-3-(3-methylsulfonyl-4-methoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



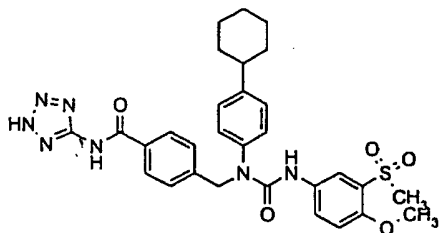
4-Methoxy-3-methylsulfonylaniline was prepared as described in Holmes, Ingold & Ingold, J. Chem. Soc., 1927, 1684-90, and the corresponding isocyanate was prepared using the triphosgene method described in example 240.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.30 (9H, s), 3.22 (3H, s), 3.90 (3H, s), 5.00 (2H, s), 7.2 (3H, m), 7.40 (2H, d), 7.45 (2H, d), 7.80 (1H, dd), 7.94 (1H, d), 8.03 (2, d), 8.48 (1H, s), 12.2 (H, s).

HPLC-MS (Method B): m/z = 578 (M+1), R<sub>t</sub> = 5.63 min.

EXAMPLE 340 (general procedure (M))

4-[1-(4-Cyclohexylphenyl)-3-(3-methylsulfonyl-4-methoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



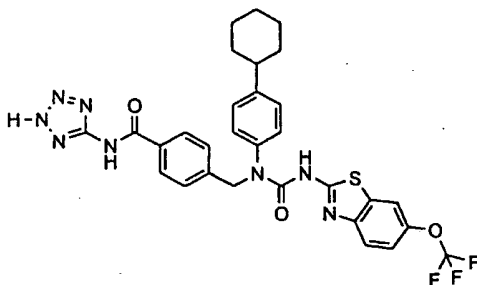
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<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.2-1.4 (5H, m), 1.55-1.8 (5H, m), 3.22 (3H, s), 3.90 (3H, s), 4.99 (2H, s), 7.2 (5H, m), 7.44 (2H, d), 7.79 (1H, dd), 7.92 (1H, d), 8.02 (2H, d), 8.47 (1H, s), 11.9 (1H, s), 12.3 (1H, s).

10 HPLC-MS (Method B): *m/z* = 604 (*M*+1), *R*<sub>t</sub> = 6.40 min.

EXAMPLE 341 (general procedure (M))

4-[1-(4-Cyclohexylphenyl)-3-(6-trifluoromethoxybenzothiazol-2-yl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



15

Using isocyanate formed in situ from (substituted) 2-aminobenzothiazole and diphosgene in pyridine:

2-Amino-6-(trifluoromethoxy)benzothiazole (334 mg, 1.43 mmol) was dissolved in pyridine (5 mL). Diphosgene (0.1 mL, 0.83 mmol) was added and the reaction mixture was stirred for 2 hours at room temperature. 4-[(4-cyclohexylphenylamino)methyl]-N-(2H-tetrazol-5-yl)benzamide (400 mg, 1.06 mmol) was added and the reaction mixture was heated to 80°C for two hours. The reaction mixture was poured into acetonitrile (50 mL) and stored at -20°C overnight and the resulting precipitate was subsequently collected by filtration to afford the title compound.

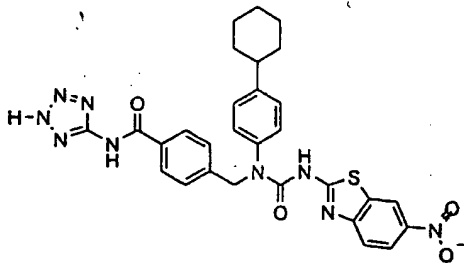
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HPLC-MS (Method D):  $R_t = 6.20$  min,  $m/z = 637$  ( $M+1$ ).

EXAMPLE 342 (general procedure (M))

- 5 4-[1-(4-Cyclohexylphenyl)-3-(6-nitrobenzothiazol-2-yl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide

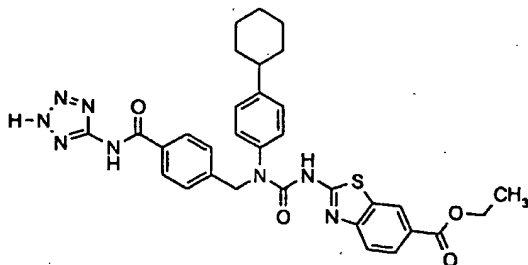


HPLC-MS (Method D):  $R_t = 5.67$  min,  $m/z = 598$  ( $M+1$ ).

10

EXAMPLE 343 (general procedure (M))

- 2-[3-(4-Cyclohexylphenyl)-3-[4-(2H-tetrazol-5-ylcarbamoyl)benzyl]ureido]benzothiazole-6-carboxylic acid ethyl ester

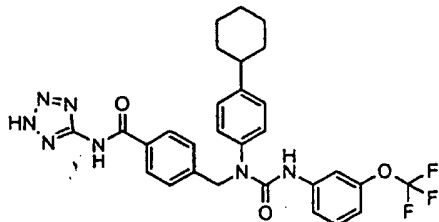


15

HPLC-MS (Method D):  $R_t = 5.83$  min,  $m/z = 625$  ( $M+1$ ).

**EXAMPLE 344 (general procedure (M))**

4-[1-(4-Cyclohexylphenyl)-3-(3-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



5

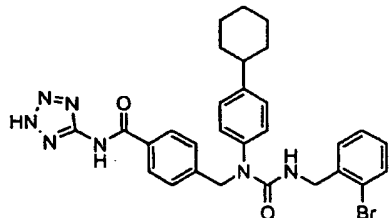
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.2-1.4 (m, 5H), 1.7-1.8 (m, 5H), 5.00 (s, 2H), 6.93 (d, 1H), 7.22 (m, 4H), 7.34 (t, 1H), 7.45 (m, 3H), 7.60 (s, 1H), 8.05 (d, 2H), 8.53 (s, 1H), 12.4 (bs, 1H).

HPLC-MS (method B):  $R_t$  = 7.93 min,  $m/z$  = 580 (M + 1).

10

**EXAMPLE 345 (general procedure (M))**

4-[3-(2-Bromobenzyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

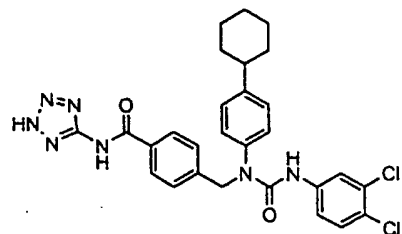


15  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.2-1.5 (m, 5H), 1.7-1.8 (m, 5H), 4.25 (d, 2H), 4.92 (s, 2H), 6.46 (m, 1H), 7.15-7.30 (m, 6H), 7.45 (m, 3H), 7.56 (d, 1H), 8.07 (d, 2H), 12.4 (s, 1H).

**EXAMPLE 346 (general procedure (M))**

4-[1-(4-Cyclohexylphenyl)-3-(3,4-dichlorophenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide

20



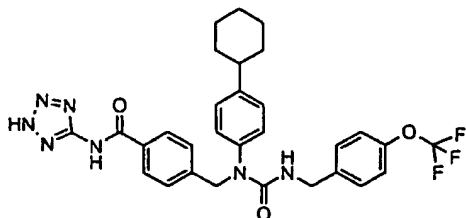
$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.3-1.4 (m, 5H), 1.7-1.8 (m, 5H), 5.00 (s, 2H), 7.22 (m, 4H), 7.45 (m, 3H), 7.83 (s, 1H), 8.04 (d, 2H), 8.53 (s, 1H), 12.4 (s, 1H).

HPLC-MS (method B):  $R_t$  = 8.07 min,  $m/z$  = 564 ( $M + 1$ ).

5

EXAMPLE 347 (general procedure (M))

4-[1-(4-Cyclohexylphenyl)-3-(4-trifluoromethoxybenzyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



10

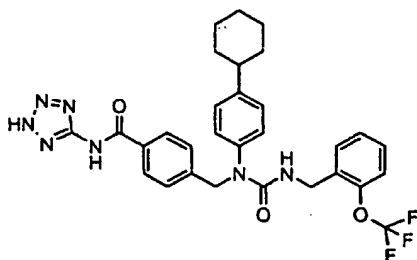
$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.2-1.4 (m, 5H), 1.7-1.8 (m, 5H), 2.57 (s, 1H), 4.28 (d, 2H), 4.91 (s, 2H), 6.57 (t, 1H), 7.14 (d, 2H), 7.22 (d, 2H), 7.29-7.40 (m, 6H), 8.02 (d, 2H), 12.3 (s, 1H).

HPLC-MS (method B):  $R_t$  = 7.68 min,  $m/z$  = 594 ( $M + 1$ ).

15

EXAMPLE 348 (general procedure (M))

4-[1-(4-Cyclohexylphenyl)-3-(2-trifluoromethoxybenzyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



20

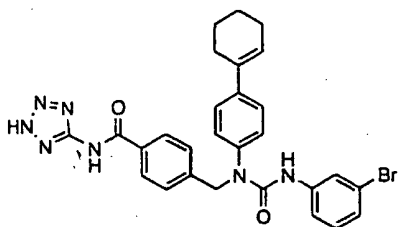
$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.2-1.4 (m, 5H), 1.7-1.8 (m, 5H), 2.55 (s, 1H), 4.34 (d, 2H), 4.91 (s, 2H), 6.44 (t, 1H), 7.17 (d, 2H), 7.22 (d, 2H), 7.29-7.42 (m, 6H), 8.02 (d, 2H), 12.3 (s, 1H).

HPLC-MS (method B):  $R_t$  = 7.72 min,  $m/z$  = 594 ( $M + 1$ ).

25

EXAMPLE 349 (general procedure (M))

4-[3-(3-Bromophenyl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



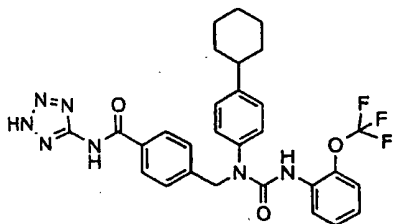
5

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.59 (m, 2H), 1.72 (m, 2H), 2.17 (m, 2H), 2.35 (m, 2H), 5.01 (s, 2H), 6.19 (t, 1H), 7.1-7.25 (m, 4H), 7.5-7.5 (m, 5H), 7.79 (s, 1H), 8.04 (d, 2H), 8.42 (s, 1H), 12.4 (s, 1H).

10 HPLC-MS (method C):  $R_t$  = 5.73 min,  $m/z$  = 574 ( $M + 1$ ).

EXAMPLE 350 (general procedure (M))

4-[1-(4-Cyclohexylphenyl)-3-(2-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



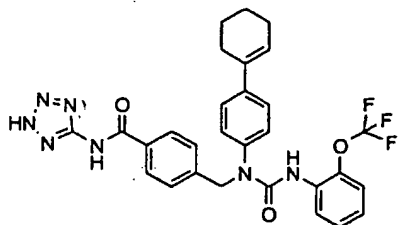
15

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.2-1.4 (m, 5H), 1.7-1.8 (m, 5H), 4.99 (s, 2H), 6.44 (t, 1H), 7.12 (t, 1H), 7.20 (s, 1H), 7.25-7.35 (m, 6H), 7.49 (d, 2H), 8.05 (d, 2H), 8.11 (d, 1H), 12.4 (s, 1H).

20 HPLC-MS (method B):  $R_t$  = 8.20 min,  $m/z$  = 580 ( $M + 1$ ).

EXAMPLE 351 (general procedure (M))

4-[1-(4-Cyclohex-1-enylphenyl)-3-(2-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



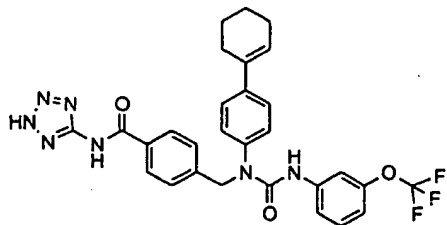
5

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.60 (m, 2H), 1.71 (m, 2H), 2.17 (m, 2H), 2.33 (m, 2H), 5.01 (s, 2H), 6.19 (m, 1H), 7.15 (t, 1H), 7.30-7.50 (m, 9H), 7.99 (d, 1H), 8.05 (d, 2H), 12.4 (s, 1H).

10 HPLC-MS (method B):  $R_t$  = 7.90 min,  $m/z$  = 578 (M + 1).

EXAMPLE 352 (general procedure (M))

4-[1-(4-Cyclohex-1-enylphenyl)-3-(3-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



15

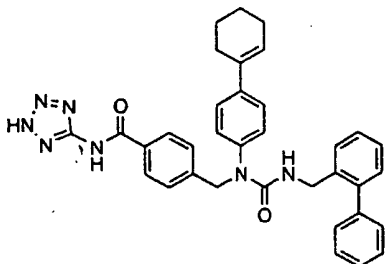
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.60 (m, 2H), 1.70 (m, 2H), 2.18 (m, 2H), 2.34 (m, 2H), 5.00 (s, 2H), 6.19 (t, 1H), 6.93 (d, 1H), 7.22 (d, 2H), 7.35 (t, 1H), 7.4-7.5 (m, 5H), 7.60 (s, 1H), 8.03 (d, 2H), 8.53 (s, 1H), 12.4 (s, 1H).

20

HPLC-MS (method B):  $m/z$  = 578 (M + 1),  $R_t$  = 7.77 min.

EXAMPLE 353 (general procedure (M))

4-[3-Biphenyl-2-ylmethyl-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



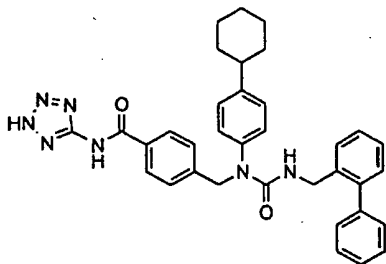
5

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.59 (m, 2H), 1.70 (m, 2H), 2.15 (m, 2H), 2.33 (m, 2H), 4.21 (d, 2H), 4.90 (s, 2H), 6.15 (t, 1H), 6.28 (t, 1H), 7.10 (d, 2H), 7.18 (d, 1H), 7.3-7.5 (m, 15H), 7.95 (s, 1H), 8.00 (d, 2H), 12.3 (s, 1H).

10 HPLC-MS (method B):  $R_t$  = 7.78 min,  $m/z$  = 584 ( $M + 1$ ).

EXAMPLE 354 (general procedure (M))

4-[3-Biphenyl-2-ylmethyl-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

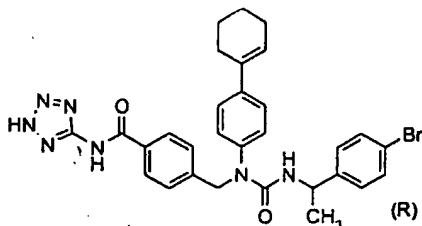


15

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.15-1.4 (m, 5H), 1.6-1.8 (m, 5H), 4.20 (d, 2H), 4.88 (s, 2H), 6.16 (t, 1H), 7.08 (d, 2H), 7.11 (m, 3H), 7.3-7.45 (m, 11H), 8.00 (d, 2H), 12.4 (s, 1H).

EXAMPLE 355 (general procedure (M))

(R)-4-[3-[1-(4-Bromophenyl)ethyl]-1-(cyclohex-1-enylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

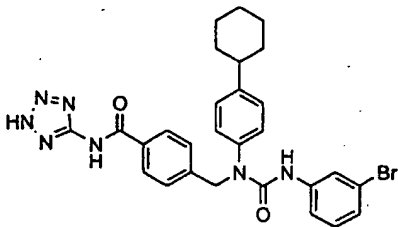


5

HPLC-MS (method B):  $R_t$  = 7.72 min,  $m/z$  = 601 ( $M + 1$ ).

EXAMPLE 356 (general procedure (M))

4-[3-(3-Bromophenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



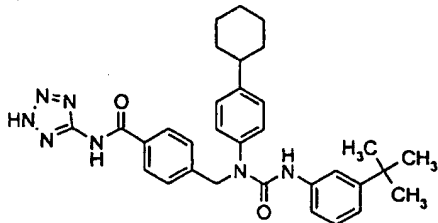
10

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.3-1.5 (m, 5H), 1.7-1.8 (m, 5H), 4.99 (s, 2H), 7.1-7.2 (m, 7H), 7.4-7.5 (m, 3H), 7.78 (s, 1H), 8.02 (d, 2H), 8.40 (s, 1H), 12.4 (s, 1H).

15 HPLC-MS (method B):  $m/z$  = 576 ( $M + 1$ ),  $R_t$  = 7.88 min.

EXAMPLE 357 (general procedure (M))

4-[1-(4-Cyclohexylphenyl)-3-(3-*tert*-butylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



20

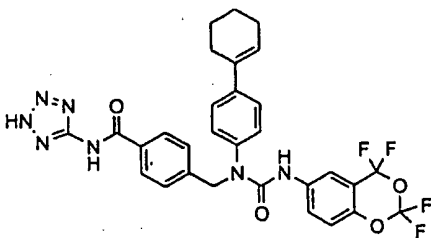
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.25 (s, 9H), 1.3-1.5 (m, 5H), 1.7-1.8 (m, 5H), 4.99 (s, 2H), 6.99 (d, 1H), 7.1-7.3 (m, 6H), 7.4-7.5 (m, 3H), 8.05 (d, 2H), 8.13 (s, 1H), 12.4 (s, 1H).

HPLC-MS (method C): *m/z* = 552 (M + 1), *R*<sub>t</sub> = 6.27 min.

5

**EXAMPLE 358 (general procedure (M))**

4-[1-(4-Cyclohex-1-enylphenyl)-3-(2,2,4,4-tetrafluoro-4*H*-benzo[1,3]dioxin-6-yl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



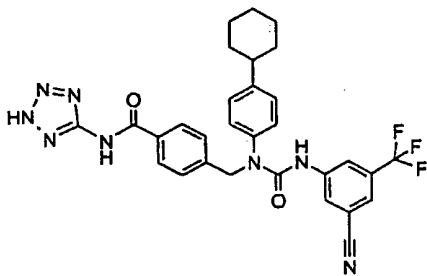
10

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.60 (2H, m), 1.70 (2H, m), 2.17 (2H, br s), 2.35 (2H, br s), 5.03 (2H, s), 6.20 (1H, s), 7.20-7.30 (2H, m), 7.35-7.50 (6H, m), 7.85, (1H, d), 8.04 (3H, m), 8.65, (1H, s), 12.40 (1H, s).

15

**EXAMPLE 359 (general procedure (M))**

4-[3-(3-Cyano-5-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



20

<sup>1</sup>H NMR (DMSO): δ 12.40 (s, 1H); 8.90 (s, 1H); 8.25 (s, 1H); 8.20 (s, 1H); 8.02 (d, 2H); 7.86 (s, 1H); 7.48 (d, 2H); 7.22 (s, 4H); 5.00 (s, 2H); 1.85-1.65 (m, 5H); 1.45-1.20 (m, 5H).

HPLC-MS (Method B): *m/z* = 589 (M+1). *R*<sub>t</sub> = 5.83 min.

25



Preparation of 3-Amino-5-trifluoromethylbenzonitrile:

Commercially available 3-nitro-5-trifluoromethylbenzoic acid (10 g, 42.5 mmol) was dissolved in toluene (50 mL) and DMF (0.5 mL) and added thionyl chloride (5 mL). The mixture was refluxed for 4 hours. After cooling to 20°C, the volatiles were removed in vacuo. The residue  
5 was re-dissolved in toluene (50 mL) and stripped. Toluene (50 mL) was added to the residue, and the solution was cooled on ice and added concentrated aqueous ammonia (10 mL). The mixture was stirred overnight and allowed to reach 20°C. 3-Nitro-5-trifluoromethylbenzamide was collected by filtration.

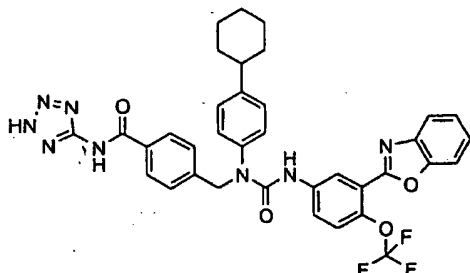
10 The above 3-nitro-5-trifluoromethylbenzamide (7.25 g) was dissolved in DMF (25 mL) and added to an ice-cooled solution of POCl<sub>3</sub> (10 mL) in DMF (20 mL). The mixture was stirred 30 min at 0°C and then heated to 40°C for 4 hours. The reaction mixture was added to ice (300 mL), stirred for 1 hour and 3-nitro-5-trifluoromethylbenzonitrile was collected by filtration.

15 3-Nitro-5-trifluoromethylbenzonitrile (1 g, 4.63 mmol) was dissolved in methanol (8 mL) and added activated charcoal (0.1 g), FeCl<sub>3</sub>·6H<sub>2</sub>O (17 mg, 0.06 mmol) and *N,N*-dimethylhydrazine (3.7 mL, 48.6 mmol). The mixture was refluxed overnight. The mixture was filtered and the volatiles removed in vacuo. The residue was purified by chromatography on silica using a  
20 mixture of heptane and ethyl acetate (4:1) as eluent affording 3-amino-5-trifluoromethylbenzonitrile.

The aniline was converted into the corresponding isocyanate by methods already described.

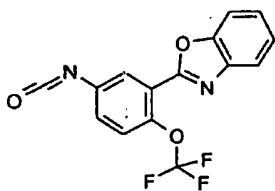
**EXAMPLE 360 (general procedure (M))**

4-[3-(3-Benzoxazol-2-yl-4-trifluoromethoxyphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



- 5  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.32-1.50 (m, 5H); 1.63-1.86 (m, 5H); 5.04 (s, 2H); 7.26 (s, 5H); 7.43-7.55 (m, 5H); 7.76-7.92 (m, 3H); 8.05 (d, 2H); 8.51 (d, 1H); 8.84 (s, 1H); 12.17 (s, 1H).

Preparation of 2-(5-isocyanato-2-trifluoromethoxyphenyl)benzoxazole:



10

- Concentrated sulphuric acid (26 mL) was added dropwise to a flask containing 26 mL of 100% nitric acid while the temperature was kept at 2-6°C. Stirring was continued at this temperature while 2-(trifluoromethoxy)benzonitrile (26.16 g, 0.1398 mol) was added dropwise. When the addition was complete, the mixture was heated at 60°C for 1 hour and poured into ice water. The precipitate was filtered off and treated with aqueous sodium hydrogen carbonate until neutral reaction. The crystals were collected and dried to afford 28.53 g (82%) of 5-nitro-2-trifluoromethoxybenzoic acid.
- 15

Mp 134-135°C.

20

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  7.79 (dd, 1H), 8.53 (dd, 1H), 8.64 (d, 1H), 14.13 (br s, 1H).

- A mixture of 5-nitro-2-trifluoromethoxybenzoic acid (6.43 g, 25.6 mmol) and 128 mg of 10% Pd/C in 10 mL of absolute ethanol was stirred in a hydrogen atmosphere overnight at room temperature. The catalyst was filtered off and the filtrate was evaporated to dryness. The re-
- 25

residue was triturated with diethyl ether and the crystals were filtered off and dried to afford 1.644 g (29%) of 5-amino-2-trifluoromethoxybenzoic acid.

Mp 196-197°C.

5

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 5.83 (br s, 2H), 6.74 (dd, 1H), 7.06 (m, 2H), 12.52 (br s, 1H).

A mixture 750 mg of 5-amino-2-trifluoromethoxybenzoic acid (750 mg, 3.39 mmol) and 2-aminophenol (370 mg, 3.39 mmol) in 10 mL of polyphosphoric acid was heated and stirred at 250°C for 3.5 hours. The mixture was poured into ice water under stirring, followed by addition of NaHCO<sub>3</sub> until pH 8. The mixture was extracted with ethyl acetate. The organic phase was washed with water twice, brine, rinsed with activated charcoal, dried over MgSO<sub>4</sub> and evaporated to give an oil, which contained two compounds, according to TLC. This mixture was dissolved in DMF and separated on semi preparative HPLC (Gilson 215 Liquid Handler), stationary phase: RP18, mobile phase: Water/MeCN gradient 95%/5% - 5%/95% to afford 216mg (22%) of 3-benzoxazol-2-yl-4-trifluoromethoxyphenylamine as crystals.

15

Mp 133-135°C.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 5.73 (br s, 2H), 6.82 (dd, 1H), 7.23 (dd, 1H), 7.44 (m, 3H), 7.82 (m, 2H).

20

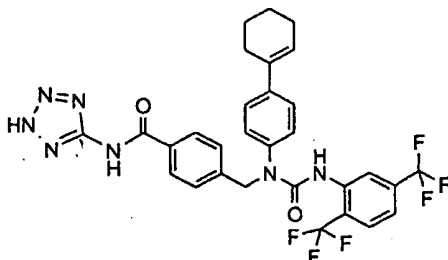
A solution of 3-benzoxazol-2-yl-4-trifluoromethoxyphenylamine (210 mg, 0.71 mmol) in 5 mL of dry toluene was stirred while 1.15 mL of 3.1N hydrochloric acid in ethyl acetate was added. The precipitate was concentrated by evaporation. Another 5 mL of toluene was added followed by evaporation. This procedure was repeated 3 times to remove excess of hydrochloric acid. The amine hydrochloride was dissolved in 5 mL of toluene and trichloromethyl chloroformate (0.853 mL, 7.1 mmol) was added. The mixture was refluxed overnight under a nitrogen atmosphere, evaporated at 70°C followed by stripping with dry toluene.

25

30 2-(5-Isocyanato-2-trifluoromethoxyphenyl)benzoxazole (160 mg, 70%) was obtained as crystals and used immediately to synthesize the title compound.

**EXAMPLE 361 (general procedure (M))**

4-[3-(2,5-Bis(trifluoromethyl)phenyl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

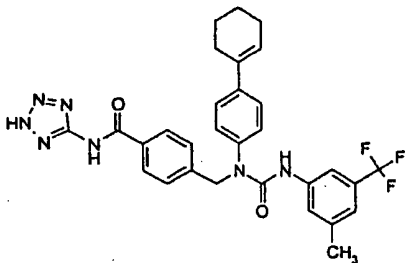
HPLC-MS (method B):  $m/z$ : 630,  $R_t$  = 8.48 min.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.54-1.62 (2H, m), 1.68-1.78 (2H, m), 2.18 (2H, broad), 2.34 (2H, broad), 5.02 (2H, s), 6.21 (1H, broad), 7.32 (2H, d), 7.48 (4H, dd), 7.65 (1H, d), 7.90 (1H, d), 8.02 (2H, d), 8.40 (1H, s), 11.95 (1H, broad).

10

**EXAMPLE 362 (general procedure (M))**

4-[1-(4-Cyclohex-1-enylphenyl)-3-(3-methyl-5-trifluoromethylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



15

HPLC-MS (method B):  $m/z$ : 576,  $R_t$  = 8.02 min.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.60 (2H, m), 1.70 (2H, m), 2.17 (2H, m), 2.32 (3H, s), 2.35 (2H, m), 5.02 (2H, s), 6.20 (s, 1H), 7.12 (1H, s), 7.24 (2H, d), 7.42 (2H, d), 7.46 (2H, d), 7.60 (1H, s), 7.74 (1H, s), 8.03 (2H, d), 8.49 (1H, s), 12.39 (1H, s).

20

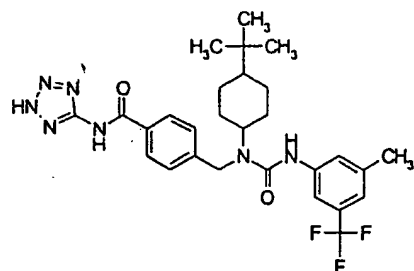
Microanalysis: calculated for  $\text{C}_{30}\text{H}_{28}\text{F}_3\text{N}_7\text{O}_2$ :

62.60% C; 4.90% H; 17.03% N. Found:

62.57% C; 4.95% H; 17.07% N.

**EXAMPLE 363 (general procedure (M))**

4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-methyl-5-trifluoromethylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

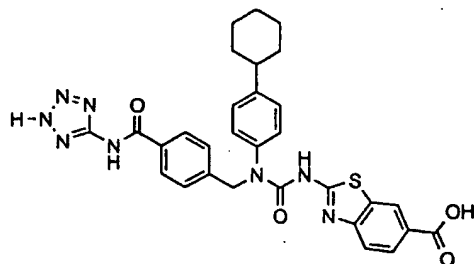


HPLC- MS (method D):  $m/z$ : 558,  $R_t$  = 5.44 min.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  0.83 (9H,s), 0.96 (1H, m), 1.14 (2H,m), 1.44 (2H,m), 1.73 (4H,m), 2.25 (3H, s), 4.04 (1H,m), 4.64 (2H,s), 7.10 (1H,s), 7.40 (2H,d), 7.59 (1H,s), 7.75 (1H,s), 8.03 (2H,d), 8.66 (1H,s), 12.49 (1H,s).

**EXAMPLE 364**

2-[3-(4-Cyclohexylphenyl)-3-[4-(2H-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzothiazole-6-carboxylic acid

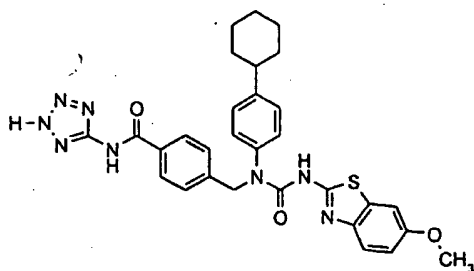


2-[3-(4-Cyclohexylphenyl)-3-[4-(2H-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzothiazole-6-carboxylic acid ethyl ester (16 mg, 0.025 mmol) was dissolved in ethanol (4 mL). Sodium hydroxide (1 mL, 4 N) was added and the reaction mixture was left at room temperature for 16 hours. Hydrochloric acid (4 mL, 1 N) was added, and the resulting precipitate was subsequently collected by filtration to afford the title compound.

HPLC-MS (Method B):  $R_t = 6.68$  min,  $m/z = 597$  ( $M+1$ ).

EXAMPLE 365 (general procedure (M))

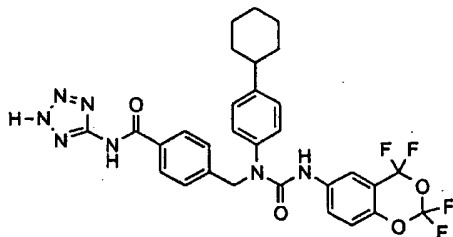
4-[1-(4-Cyclohexylphenyl)-3-(6-methoxybenzothiazol-2-yl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



HPLC-MS (Method D):  $R_t = 5.53$  min,  $m/z = 583$  ( $M+1$ ).

10 EXAMPLE 366 (general procedure (M))

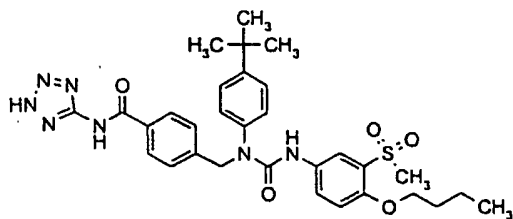
4-[1-(4-Cyclohexylphenyl)-3-(2,2,4,4-tetrafluoro-4H-benzo[1,3]dioxin-6-yl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



15 HPLC-MS (Method D):  $R_t = 6.17$  min,  $m/z = 626$  ( $M+1$ ).

EXAMPLE 367 (general procedure (M))

4-[3-(4-Butoxy-3-methylsulfonylphenyl)-1-(4-tert-butylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



4-Butoxy-3-methylsulfonylaniline was prepared from 4-methoxy-3-methylsulfonylaniline as described in Gitis, Malinovskii, Prokhoda & Sribnaya J. Gen. Chem. USSR (Engl. Transl.) 1960 (30), 3045-7, and the corresponding isocyanate was prepared using the triphosgene method described in example 240.

5

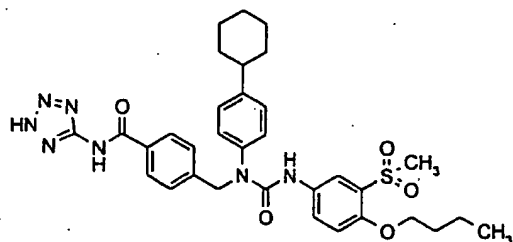
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  4.11 (2H, t), 4.96 (2H, s), 7.18 (3H, m), 7.37 (5H, m), 7.9 (3H, m), 8.45 (1H, s).

HPLC-MS (Method B):  $m/z$  = 620 (M+1),  $R_t$  = 6.97 min.

10

EXAMPLE 368 (general procedure (M))

4-[3-(4-Butoxy-3-methylsulfonylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



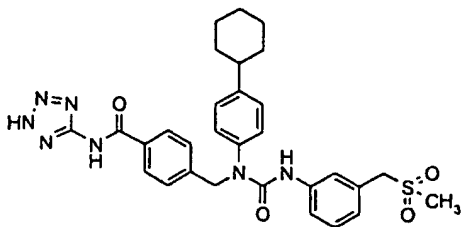
15

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.94 (3H, t), 1.3-1.55 (8H, m), 1.7-1.8 (8H, m), 3.22 (3H, s), 4.10 (2H, t), 4.98 (2H, s), 7.2-7.3 (5H, m), 7.46 (2H, d), 7.78 (1H, dd), 7.93 (1H, d), 8.05 (2H, d), 8.45 (1H, s), 12.4 (1H, s).

20 HPLC-MS (Method B):  $m/z$  = 646 (M+1),  $R_t$  = 7.70 min.

EXAMPLE 369 (general procedure (M))

4-[1-(4-Cyclohexylphenyl)-3-(3-methylsulfonylmethylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



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3-Methylsulfonylmethylphenyl isocyanate was prepared as follows:

m-Nitrobenzyl chloride (4.21 g, 24.5 mmol) was dissolved in DMF (40 mL) and added sodium methanesulfinate (3.00 g, 29.4 mmol) and the resulting mixture was stirred at room temperature for 16 hours. After evaporation of the solvent in vacuo the residue was partitioned between water (100 mL) and ethyl acetate (100 mL). The aqueous phase was extracted with ethyl acetate (100 mL) and the combined organic phases were dried (MgSO<sub>4</sub>) and evaporated in vacuo to afford 4.45 g (84 %) 1-methylsulfonylmethyl-3-nitrobenzene.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.92 (3H, s), 4.39 (2H), 7.65 (1H, t), 7.80 (1H, d), 8.29 (2H, m).

1-Methylsulfonylmethyl-3-nitrobenzene (4.70 g, 21.8 mmol) was added ethanol (70 mL) and the mixture was heated to reflux. At reflux the mixture was added SnCl<sub>2</sub> dihydrate (24.6 g, 109 mmol) and heating at reflux was continued for 1 hour. After cooling, the mixture was poured into ice/water (200 mL) and neutralised (to pH 7) with 1 N sodium hydroxide. The mixture was filtered through celite, and the filter cake was washed with ethyl acetate. The phases from the combined filtrate and washings were separated, and the aqueous phase was extracted with ethyl acetate (2 x 150 mL). The combined organic phases were dried (MgSO<sub>4</sub>) and evaporated in vacuo to afford 2.23 g (55%) 3-(methylsulfonylmethyl)aniline.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.77 (3H, s), 3.76 (2H, bs), 4.15 (2H, s), 6.75 (3H, m), 7.18 (1H, t).

The corresponding isocyanate was prepared using the triphosgene method described in example 240.

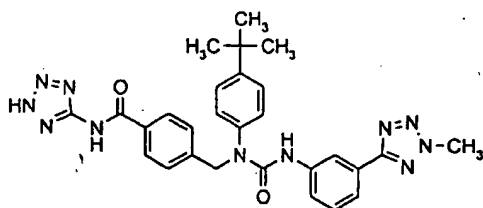
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.2-1.4 (6H, m), 1.7-1.8 (5H, m), 2.91 (3H, s), 4.40 (2H, s), 5.00 (2H, s), 6.99 (1H, d), 7.2-7.3 (5H, m), 7.46 (4H, m), 8.03 (2H, d), 8.32 (1H, s), 12.4 (1H, s).

HPLC-MS (Method B): *m/z* = 588 (M+1), *R*<sub>t</sub> = 7.48 min.



EXAMPLE 370 (general procedure (M))

4-(1-(4-*tert*-Butylphenyl)-3-[3-(2-methyl-2*H*-tetrazol-5-yl)phenyl]ureidomethyl)-*N*-(2*H*-tetrazol-5-yl)benzamide



5

3-(2-Methyl-2*H*-tetrazol-5-yl)phenyl isocyanate was prepared as follows:

m-Nitrocyanobenzene (10 g, 67.5 mmol) was dissolved in DMF and ammonium chloride (7.2 g, 135 mmol) and sodium azide (8.8 g, 135 mmol) were added and the resulting mixture was stirred at 125°C for 16 hours. After cooling to room temperature, the mixture was poured into water (1 L), acidified with 1 N hydrochloric acid and filtered immediately. The mother liquor was left for 1 hour and filtered and the solid was washed with water and dried by suction to afford 9.3 g (72%) 5-(3-nitrophenyl)-2*H*-tetrazole.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 7.94 (1H, t), 8.43 (1H, ddd), 8.48 (1H, dt), 8.85 (1H, t).

15

The above 5-(3-nitrophenyl)-2*H*-tetrazole (6.52 g, 34 mmol) was dissolved in DMF (75 mL) and potassium carbonate (14 g) and iodomethane (2.23 mL, 36 mmol) were added and the resulting mixture was stirred at room temperature for 16 hours. After evaporation in vacuo, the mixture was partitioned between water (150 mL) and ethyl acetate (100 mL). The aqueous phase was extracted with ethyl acetate (100 mL), and the combined organic phases were dried (MgSO<sub>4</sub>) and evaporated in vacuo. The residue was washed with a mixture of heptane and diethyl ether to afford 7 g (100%) of a mixture of 1- and 2-methyl-5-(3-nitrophenyl)tetrazole. These isomers were separated using column chromatography.

2-Methyl-5-(3-nitrophenyl)-2*H*-tetrazole (2.12 g, 10 mmol) was added ethanol (50 mL) and heated to reflux. At reflux, the mixture was added SnCl<sub>2</sub> dihydrate (11.6 g, 52 mmol) and the mixture was heated at reflux for 2 hours. After cooling, the mixture was poured into ice/water (200 mL) and neutralised (to pH 7) with 1 N sodium hydroxide. The mixture was filtered through celite, and the filter cake was washed with ethyl acetate. For the combined filtrate and washings the phases were separated and the aqueous phase was extracted with ethyl

30

acetate (2 x 250 mL). The combined organic phases were dried (MgSO<sub>4</sub>) and evaporated in vacuo to afford 3-(2-methyl-2H-tetrazol-5-yl)aniline.

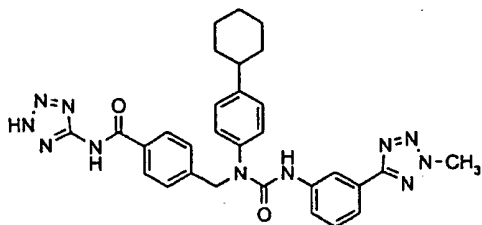
<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.80 (2H, bs), 4.40 (3H, s), 6.79 (1H, ddd), 7.28 (1H, dd), 7.47 (1H, m),  
5 7.51 (1H, dt).

The corresponding isocyanate was prepared using the triphosgene method described in example 240.

10 HPLC-MS (Method B): m/z = 552 (M+1), R<sub>t</sub> = 6.58 min.

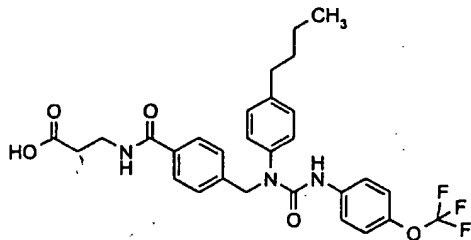
EXAMPLE 371 (general procedure (M))

4-{1-(4-Cyclohexylphenyl)-3-[3-(2-methyl-2H-tetrazol-5-yl)phenyl]ureidomethyl}-N-(2H-tetrazol-5-yl)benzamide



<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.2-1.4 (6H, m), 1.6-1.8 (5H, m), 4.40 (3H, s), 5.01 (2H, s), 7.22 (4H, m), 7.40 (1H, t), 7.45 (3H, m), 7.65 (2H, d), 8.01 (2H, d), 8.23 (1H, s), 8.52 (1H, s), 12.0 (1H, bs).

HPLC-MS (Method B): m/z = 578 (M+1), R<sub>t</sub> = 5.37 min.

**EXAMPLE 372****3-{4-[1-(4-Butylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid**

5

4-Formylbenzoic acid (15 g, 100 mmol) was dissolved in DMF (250 mL) and 1-hydroxy-benzotriazole (14.9 g, 110 mmol) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (21.1 g, 110 mmol) were added and the resulting mixture was stirred at room temperature for 30 minutes. Triethylamine (34.8 mL, 250 mmol) and  $\beta$ -alanine methyl ester hydrochloride (15.4 g, 110 mmol) were added and the resulting mixture was stirred at room temperature for 1 hour. More triethylamine (17.4 mL) and  $\beta$ -alanine methyl ester hydrochloride (7.7 g) were added and the mixture was stirred at room temperature for 16 hours. The mixture was concentrated in vacuo and the residue was partitioned between ethyl acetate (200 mL) and water (200 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated to afford 16.2 g (70%) of 3-(4-formylbenzoylamino)propionic acid methyl ester as an oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.70 (2H, t), 3.69 (3H, s), 3.70 (2H, q), 7.68 (1H, bt), 7.9-8.0 (4H, m), 10.1 (1H, s).

20 The above propionic acid methyl ester (2.0 g, 8.5 mmol) was dissolved in DMF (20 mL) and triethyl orthoformate (10 mL), glacial acetic acid (1 mL), sodium cyanoborohydride (0.81 g, 12.8 mmol) and 4-butylaniline 1.27 g, 8.5 mmol) were added and the resulting mixture was stirred at room temperature for 16 hours. The mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (100 mL) and washed with saturated aqueous sodium chloride (3 x 100 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and heptane (3:1) to afford 1.54 g (49%) of 3-{4-[(4-butylphenylamino)methyl]-benzoylamino}propionic acid methyl ester as an oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.92 (3H, t), 1.33 (2H, m), 1.54 (2H, pentet), 2.50 (2H, t), 2.67 (2H, t), 3.72 (5H, m), 4.38 (2H, s), 6.55 (2H, d), 6.83 (1H, bt), 6.98 (2H, d), 7.43 (2H, d), 7.74 (2H, d).

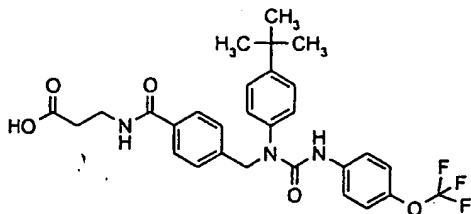
The above propionic acid methyl ester (0.5 g, 1.4 mmol) was dissolved in acetonitrile (10 mL) and added N,N-diisopropylethylamine (232 μL, 1.4 mmol) and 4-(trifluoromethoxy)phenylisocyanate (308 μL, 2.0 mmol) and the resulting mixture was stirred at room temperature for 16 hours. More 4-(trifluoromethoxy)phenylisocyanate (308 μL, 2.0 mmol) was added and the mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate (50 mL) and washed with water (3 x 50 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and heptane (1:1) containing 1% glacial acetic acid. This afforded 0.53 g (69%) of 3-{4-[1-(4-butylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid methyl ester as an oil.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.98 (3H, t), 1.30 (2H, m), 1.55 (2H, quintet), 2.60 (4H, m), 3.48 (2H, q), 3.61 (3H, s), 4.95 (2H, s), 7.15 (4H, m), 7.22 (2H, d), 7.33 (2H, d), 7.54 (2H, d), 7.75 (2H, d), 8.30 (1H, s), 8.49 (1H, t).

HPLC-MS (Method B): R<sub>t</sub> = 8.00 min, m/z = 572 (M+1).

The above propionic acid methyl ester (0.53 g, 0.93 mmol) was dissolved in 1,4-dioxane (50 mL). 4N aqueous sodium hydroxide (6 mL) was added and the resulting mixture was stirred at room temperature for 4 hours. Glacial acetic acid (10 mL) was added and the mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate (30 mL) and washed with water (30 mL). The aqueous phase was extracted with ethyl acetate (2 x 30 mL), and the combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated to afford 0.49 g (95%) of the title compound as an oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.94 (3H, t), 1.37 (2H, m), 1.62 (2H, quintet), 2.64 (2H, t), 2.71 (2H, t), 3.73 (5H, m), 4.94 (2H, s), 6.29 (1H, s), 6.87 (1H, t), 7.04 (2H, d), 7.09 (2H, d), 7.21 (2H, d), 7.29 (2H, d), 7.34 (2H, d), 7.68 (2H, d).

**EXAMPLE 373****3-{4-[1-(4-*tert*-Butylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid**

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The above 3-(4-formylbenzoylamino)propionic acid methyl ester (2.0 g, 8.5 mmol) was dissolved in DMF (20 mL). Triethyl orthoformate (10 mL), glacial acetic acid (1 mL), sodium cyanoborohydride (0.81 g, 12.8 mmol) and 4-*tert*-butylaniline 1.27 g, 8.5 mmol) were added and the resulting mixture was stirred at room temperature for 16 hours. The mixture was added saturated aqueous sodium chloride (100 mL) and the mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (3 x 100 mL). The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and heptane (1:1) to afford 0.87 g (30%) of 3-{4-[(4-*tert*-butylphenyl-amino)methyl]benzoylamino}propionic acid methyl ester as an oil.

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<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.28 (9H, s), 2.67 (2H, t), 3.73 (5H, m), 4.04 (1H, s), 4.38 (2H, s), 6.57 (2H, d), 6.83 (2H, d), 7.19 (2H, d), 7.44 (2H, d), 7.73 (2H, d).

20 HPLC-MS (Method B): R<sub>t</sub> = 6.63 min, m/z = 369 (M+1).

The above propionic acid methyl ester (0.82 g, 2.2 mmol) was dissolved in acetonitrile (15 mL) and added *N,N*-diisopropylethylamine (378 μL, 2.2 mmol) and 4-(trifluoromethoxy)-phenylisocyanate (500 μL, 3.3 mmol). The resulting mixture was stirred at room temperature for 5 hours and at reflux for 16 hours. The cooled reaction mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (50 mL) and washed with water (2 x 50 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was crystallised from a mixture of ethyl acetate and heptane (1:1) containing 1% glacial acetic acid to afford 0.40 g (32%) of 3-{4-[1-(4-*tert*-butylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid methyl ester as a solid.

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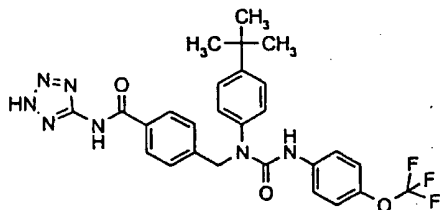
<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.34 (9H, s), 2.67 (2H, t), 3.72 (5H, m), 4.94 (2H, s), 6.30 (1H, s), 6.80 (1H, t), 7.1 (4H, m), 7.3-7.4 (4H, m), 7.43 (2H, d), 7.70 (2H, d).

The above propionic acid methyl ester (0.25 g, 0.44 mmol) was dissolved in 1,4-dioxane (25 mL). 4N aqueous sodium hydroxide (6 mL) was added and the mixture was stirred at room temperature for 16 hours. 36% aqueous hydrochloric acid (10 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was crystallised from a mixture of diethyl ether and heptane to afford 0.10 g (42%) of the title compound as a solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.33 (9H, s), 2.70 (2H, t), 3.71 (2H, q), 4.95 (2H, s), 6.32 (1H, s), 6.88 (1H, t), 7.1 (4H, m), 7.28 (2H, d), 7.35 (2H, d), 7.43 (2H, ), 7.68 (2H, d).

#### EXAMPLE 374

4-[1-(4-*tert*-Butylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



4-Formylbenzoic acid methyl ester (10.6 g, 64 mmol) was dissolved in methanol (200 mL).

4-*tert*-Butylaniline (9.61 g, 64 mmol) was added and the resulting suspension was refluxed for 15 minutes. After cooling to room temperature, TFA (5.18 mL, 68 mmol) was added followed by portion wise addition of sodium cyanoborohydride (3.26 g, 52 mmol). The resulting mixture was stirred at room temperature for 2 hours and concentrated in vacuo. The residue was partitioned between ethyl acetate (200 mL) and 1N aqueous sodium hydroxide (150 and 100 mL). The organic phase was dried (MgSO<sub>4</sub>) and evaporated in vacuo to afford 19.0 g (99%) of 4-[(4-*tert*-butylphenylamino)methyl]benzoic acid methyl ester as a solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.28 (9H, s), 3.92 (3H, s), 4.39 (2H, s), 6.57 (2H, d), 7.20 (2H, d), 7.44 (2H, d), 8.00 (2H, d).

The above benzoic acid methyl ester (0.73 g, 2.44 mmol) was dissolved in acetonitrile (7 mL) and 4-trifluoromethoxyphenylisocyanate (405  $\mu$ L, 2.68 mmol) was added. The resulting mixture was stirred at room temperature for 3 hours and then refluxed for 1.5 hour. After cooling and concentration in vacuo, the residue was purified by column chromatography on silica gel, eluting first with a mixture of ethyl acetate and heptane (1:6), then with a mixture of ethyl acetate and heptane (1:3) to afford 1.14 g (94%) of 4-[1-(4-*tert*-butylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid methyl ester as an oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.35 (9H, s), 3.91 (3H, s), 4.97 (2H, s), 6.30 (1H, s), 7.1 (4H, m), 7.32-7.43 (6H, m), 7.96 (2H, d).

TLC:  $R_f$  = 0.11 ( $\text{SiO}_2$ ; ethyl acetate/heptane (1:6)).

HPLC-MS (Method B):  $R_t$  = 9.05 min,  $m/z$  = 501 ( $M+1$ ).

The above ureidomethyl-benzoic acid methyl ester (1.14 g, 2.28 mmol) was dissolved in 1,4-dioxane (25 mL) and added 1N aqueous sodium hydroxide (5 mL). The resulting mixture was stirred at room temperature for 1 hour. Ethanol (15 mL) and 1N aqueous sodium hydroxide (5 mL) were added and the resulting mixture was stirred at room temperature for 16 hours.

The mixture was concentrated in vacuo and partitioned between 1N hydrochloric acid (100 mL) and ethyl acetate (2 x 50 mL). The combined organic phases were dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to afford 847 mg (76%) of 4-[1-(4-*tert*-butylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid as a solid.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.33 (9H, s), 3.91 (3H, s), 4.97 (2H, s), 6.30 (1H, s), 7.1 (4H, m), 7.33 (2H, d), 7.43 (4H, m), 8.03 (2H, d).

HPLC-MS (Method B):  $R_t$  = 8.25 min,  $m/z$  = 487 ( $M+1$ ).

The above ureidomethyl-benzoic acid (508 mg, 1.04 mmol) was dissolved in dichloromethane (20 mL) and *N,N*-diisopropylethylamine (546  $\mu$ L, 3.13 mmol) and 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (321 mg, 1.15 mmol) were added. The resulting mixture was stirred at room temperature for 30 minutes. 5-Aminotetrazole hydrate (118 mg, 1.15 mmol) was added and the resulting mixture was stirred at room temperature for 16 hours. The mixture was partitioned between water (200 mL) and ethyl

acetate (2 x 100 mL). The combined organic phases were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and heptane (1:1), containing 1% acetic acid. This afforded 194 mg (34%) of the title compound as a solid.

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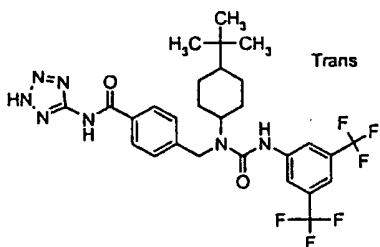
$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.33 (9H, s), 3.91 (3H, s), 5.01 (2H, s), 6.35 (1H, s), 7.10 (2H, d), 7.14 (2H, d), 7.36 (2H, d), 7.45 (2H, d), 7.58 (2H, d), 8.22 (2H, d), 12.3 (1H, s).

HPLC-MS (Method B):  $R_t$  = 7.95 min,  $m/z$  = 554 ( $M+1$ ).

10

#### EXAMPLE 375

4-[3-(3,5-Bis(trifluoromethyl)phenyl)-1-(*trans*-4-*tert*-butylcyclohexyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



15

This compound was prepared similarly as described in example 374 starting from *trans*-4-[(4-*tert*-butylcyclohexylamino)methyl]benzoic acid methyl ester (prepared as described in general procedure (K), step 1) followed by reaction with 3,5-bis(trifluoromethyl)phenyl isocyanate, hydrolysis and coupling with 5-aminotetrazole.

20

HPLC-MS (method B):  $m/z$ : 612.  $R_t$  = 8.38 min.

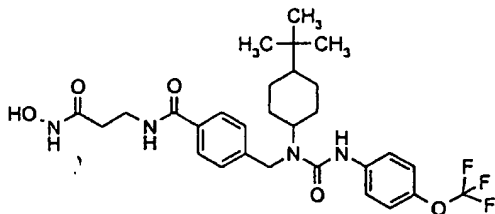
$^1\text{H}$  NMR ( $\text{DMSO}_d$ ):  $\delta$  0.83 (9H,s), 0.96 (1H,m), 1.14 (2H,m), 1.44 (2H,m), 1.73 (4H,m), 4.09 (1H,m), 4.68 (2H,s), 7.45 (2H,d), 7.63 (1H,s), 8.07 (2H,d), 8.29 (2H,s), 9.08 (1H,s), 12.49 (1H,s).

25



**EXAMPLE 376**

4-[1-(trans-4-tert-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2-hydroxycarbamoyl)ethyl]benzamide



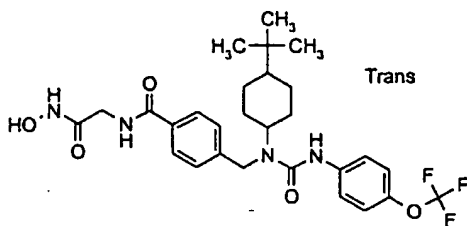
5

3-[4-[1-(4-tert-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino]-propionic acid (prepared as described in example 92; 0.2 g, 0.36 mmol) was dissolved in DMF (5 mL) and 1-hydroxybenzotriazole (53 mg, 0.39 mmol) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (75 mg, 0.39 mmol) were added and the resulting mixture was stirred at room temperature for 30 minutes. The mixture was cooled to 0°C and *N,N*-diisopropylethylamine (85 µL, 0.50 mmol) and *O*-(trimethylsilyl)hydroxylamine (60 µL, 0.50 mmol) were added and the mixture was stirred at room temperature for 16 hours. The mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (50 mL) and was washed with a saturated aqueous solution of sodium chloride (50 mL). The aqueous phase was extracted with ethyl acetate (2 x 50 mL) and the combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and glacial acetic acid (9:1). This afforded 95 mg (46%) of the title compound as a solid.

20 HPLC-MS (Method B): *R*<sub>t</sub> = 7.32 min, *m/z* = 579 (*M* + 1).

**EXAMPLE 377**

4-[1-(trans-4-tert-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-hydroxycarbamoylmethyl-benzamide



25

This compound was prepared from 3-{4-[1-(*trans*-4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}acetic acid (example 95), by coupling this compound with O-trimethylsilylhydroxylamine using standard peptide coupling conditions as described in the art.

5

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  10.60 (1H, s), 8.78 (1H, s), 8.65 (1H, t), 8.52 (1H, s), 7.80 (2H, d), 7.55 (2H, d), 7.34 (2H, d), 7.23 (2H, d), 4.60 (2H, broad), 4.05 (1H, m), 3.75 (2H, d), 1.80-0.85 (10H, m), 0.80 (9H, s).

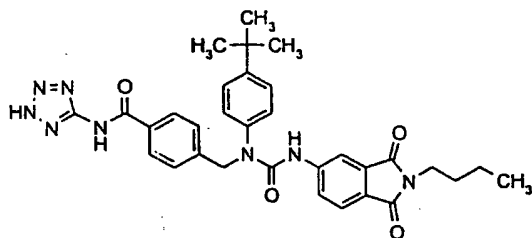
10 Micro analysis. Calculated for  $\text{C}_{28}\text{H}_{35}\text{F}_3\text{N}_4\text{O}_5$ ,  $0.75\text{H}_2\text{O}$ :

C, 58.17%; H, 6.36%; N, 9.69%. Found:

C, 58.29%; H, 6.28%; N, 9.97%.

#### EXAMPLE 378

15 4-[3-(2-Butyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-1-(4-*tert*-butylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



To a solution of 4-nitrophthalimide (7.20 g, 37.5 mmol) and n-bromobutane (25.5 g; 186 mmol) in DMF (50 mL) was added potassium carbonate (10.0 g; 72.5 mmol) and the resulting mixture was heated to 100°C for 16 hours. The reaction mixture was cooled to room temperature and partitioned between water (200 mL) and ethyl acetate (200 mL). The organic layer was separated, washed once with brine and dried with anhydrous  $\text{Na}_2\text{SO}_4$ . The solvent was removed in vacuo by rotary evaporation to leave *N*-butyl-4-nitrophthalimide as an oil, which crystallised upon standing. Yield: 9.37 g (100%).

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.91 (t, 3H); 1.31 (m, 2H); 1.60 (m, 2H); 3.62 (t, 2H); 8.11 (d, 1H); 8.47 (d, 1H); 8.61 (dd, 1H).

30 A solution of *N*-butyl-4-nitrophthalimide (1.45 g, 5.8 mmol) in methanol (30 mL) was added drop wise to a well stirred solution of sodium dithionite (6.50 g, 37.1 mmol) and sodium car-

bonate (3.22 g, 30.5 mmol) in water (40 mL), while the temperature was maintained at 70°C. After addition, heating at 70°C was continued for a further 30 minutes, then the reaction mixture was allowed to cool to room temperature. The reaction volume was reduced to one third by rotary evaporation, and the residual water solution was extracted with diethyl ether (2 x 50 mL). The combined organic phases were dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, and then taken to dryness. The residual oil was recrystallised from ethanol/water to give 750 mg (59%) of *N*-butyl-4-aminophthalimide.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.89 (t, 3H); 1.26 (m, 2H); 1.53 (m, 2H); 3.48 (t, 2H); 6.44 (bs, 2H); 6.78 (dd, 1H); 6.92 (d, 1H); 7.46 (d, 1H).

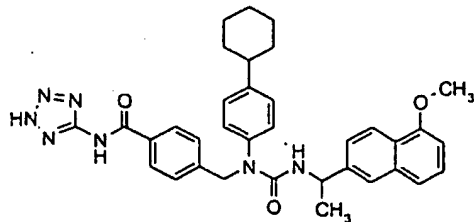
*N*-Butyl-4-aminophthalimide (100 mg, 0.46 mmol) was suspended in toluene (2 mL), and bis(trichloromethyl)carbonate (50 mg, 0.17 mmol) was added. The mixture was heated to reflux for 1 hour, then cooled and taken to dryness by rotary evaporation. The solid residue was re-dissolved in DMF (2 mL). 4-[(4-*tert*-Butylphenylamino)methyl]-*N*-2*H*-tetrazol-5-yl)benzamide (161 mg, 0.46 mmol) was added and the mixture heated to 100°C for 2 hours. After cooling to room temperature, water (3 mL) was added and the precipitated gum collected by filtration. Recrystallisation from acetonitrile afforded the title compound as a white powder. Yield: 20 mg (30%).

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.88 (t, 3H); 1.25 (m, 2H); 1.28 (s, 9H); 1.55 (m, 2H); 3.54 (t, 2H); 5.03 (s, 2H); 7.25 (d, 2H); 7.42 (d, 2H); 7.48 (d, 2H); 7.72 (d, 1H); 7.80 (d, 1H); 8.02 (s, 1H); 8.04 (d, 2H); 8.95 (s, 1H); 12.26 (bs, 1H).

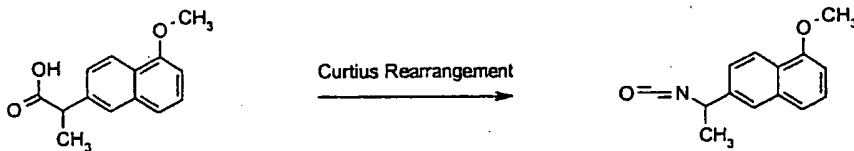
HPLC-MS (method B): 595.4 (M+1). *R*<sub>t</sub> = 7.68 min.

#### EXAMPLE 379

4-{1-(4-Cyclohexylphenyl)-3-[1-(5-methoxynaphthalen-2-yl)ethyl]ureidomethyl}-*N*-(2*H*-tetrazol-5-yl)benzamide



The isocyanate was prepared *in situ* via a Curtius rearrangement of the corresponding carboxylic acid:



5

2-(5-Methoxynaphthalen-2-yl)propionic acid (0.26 g, 1.12 mmol) was dissolved in toluene (10 mL). Triethylamine (0.52 mL) was added followed by diphenylphosphoryl azide (0.40 mL, 1.86 mmol). The mixture was stirred for 2 hours at 25°C and 4-[(4-cyclohexylphenylamino)-methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide (0.14 g, 0.37 mmol) was added. Stirring was continued at 25°C for 16 hours then at 100°C overnight. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel using a mixture of heptane and ethylacetate (1:1) as eluent to afford the title compound.

10

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 12.40 (s, 1H); 8.05 (d, 2H); 7.72 (d, 2H); 7.62 (s, 1H); 7.45-7.35 (m, 3H); 7.28 (s, 1H); 7.25-7.10 (m, 5H); 5.05 (m, 1H); 4.93 (d, 2H); 3.86 (s, 3H); 1.75-1.65 (m, 4H); 1.50-1.15 (m, 9H)

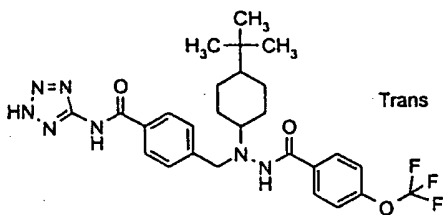
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HPLC-MS (Method B): *m/z* = 604 (*M*+1). *R*<sub>t</sub> = 8.08 min.

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#### EXAMPLE 380

4-[*N*-(*trans*-4-*tert*-Butylcyclohexyl)-*N'*-(4-trifluoromethoxybenzoyl)hydrazinomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



25

*Trans*-4-trifluoromethoxybenzoic acid *N'*-(4-*tert*-butylcyclohexyl)hydrazide (350 mg, 1.0 mmol) and methyl 4-(bromomethyl)benzoate (220 mg, 1.0 mmol) were dissolved in DMF (5.0 mL). Sodium hydrogen carbonate (300 mg) was added, and the mixture was stirred for 16 hours under a nitrogen atmosphere at ambient temperature. Water (30 mL) was added and

the mixture was extracted with diethyl ether (2 x 25 mL). The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub> and evaporated in vacuo to afford methyl 4-[*N*-(4-*tert*-butylcyclohexyl)-*N'*-(4-trifluoromethoxybenzoyl)hydrazinomethylbenzoate as white crystals. Yield: 430 mg (85%).

- 5    <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.82 (s, 9H); 0.95 (m, 3H); 1.23 (m, 2H); 1.78 (m, 2H); 2.06 (m, 2H); 3.82 (s, 3H); 4.14 (s, 2H); 7.38 (d, 2H); 7.54 (d, 2H); 7.71 (d, 2H); 7.85 (d, 2H); 9.24 (s, 1H).

- Methyl 4-[*N*-(4-*tert*-butylcyclohexyl)-*N'*-(4-trifluoromethoxybenzoyl)hydrazinomethylbenzoate (400 mg, 0.78 mmol) was dissolved in methanol (40 mL) by gentle heating. After cooling to room temperature, aqueous sodium hydroxide (4 mL; 4N) was added. The mixture was  
10    heated to reflux for 2 hours, then allowed to cool to ambient temperature. Acetic acid (3.0 mL) was added before the solvent was removed in vacuo. Water (30 mL) was added to the residue, and insoluble material was collected by filtration. Recrystallisation from acetonitrile afforded 4-[*N*-(4-*tert*-butylcyclohexyl)-*N'*-(4-trifluoromethoxybenzoyl)hydrazinomethylbenzoic  
15    acid. Yield: 320 mg (83%).

- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.82 (s, 9H); 0.96 (m, 3H); 1.24 (m, 2H); 1.78 (m, 2H); 2.05 (m, 2H); 2.85 (t, 1H); 4.13 (s, 2H); 7.38 (d, 2H); 7.50 (d, 2H); 7.72 (d, 2H); 7.82 (d, 2H); 9.26 (s, 1H).  
20    HPLC-MS (method B): 493.2 (M+1). R<sub>t</sub> = 7.92 min.

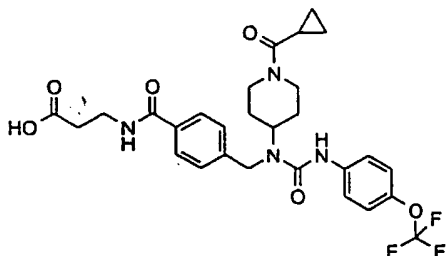
- 4-[*N*-(4-*tert*-Butylcyclohexyl)-*N'*-(4-trifluoromethoxybenzoyl)hydrazinomethylbenzoic acid (264 mg; 0.54 mmol), *N*-hydroxybenzotriazole monohydrate (82 mg, 0.54 mmol) and *N*-ethyl-*N'*-3-dimethylaminopropylcarbodiimide hydrochloride (105 mg, 0.54 mmol) were dissolved in DMF  
25    (4.0 mL). The mixture was stirred at room temperature for 30 minutes, and then 5-amino-tetrazole monohydrate (100 mg; 0.96 mmol) was added. The reaction mixture was then left stirring at ambient temperature for 48 hours. The mixture was poured in water (40 mL), and the precipitated material collected by filtration. After several washes with water, the material was dried in vacuo to afford the title compound as a white powder. Yield: 257.2 mg; (86%).

- 30    <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.82 (s, 9H); 0.98 (m, 3H); 1.25 (m, 2H); 1.80 (m, 2H); 2.07 (m, 2H); 4.16 (s, 2H); 7.38 (d, 2H); 7.59 (d, 2H); 7.73 (d, 2H); 8.02 (d, 2H); 9.26 (s, 1H); 12.27 (bs, 1H).

- 35    HPLC-MS (method B): 560.4 (M+1). R<sub>t</sub> = 7.77 min.

EXAMPLE 381

3-{4-[1-(1-Cyclopropanecarbonyl)piperidin-4-yl]-3-(4-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino}propionic acid



4-[1-[4-(2-Methoxycarbonylethylcarbamoyl)benzyl]-3-(4-trifluoromethoxyphenyl)ureido]-piperidine-1-carboxylic acid *tert*-butyl ester

4-[1-[4-(2-Methoxycarbonylethylcarbamoyl)benzyl]-3-(4-trifluoromethoxyphenyl)ureido]-piperidine-1-carboxylic acid *tert*-butyl ester was prepared in analogy with previously described methods (reductive amination using 4-aminopiperidine-1-carboxylic acid *tert*-butyl ester).

3-{4-[1-Piperidin-4-yl]-3-(4-trifluoromethoxyphenyl)ureidomethyl}benzoylamino}propionic acid methyl ester hydrochloride

The Boc-protecting group was removed by adding 20 mL HCl in ethyl acetate (2M) to a suspension of 4-[1-[4-(2-methoxycarbonylethylcarbamoyl)benzyl]-3-(4-trifluoromethoxy-phenyl)-ureido]piperidine-1-carboxylic acid *tert*-butyl ester (2.60 g) in 25 mL ethyl acetate. Stirring overnight at 25°C followed by evaporation of the solvent afforded the desired compound.

3-{4-[1-(1-Cyclopropanecarbonyl)piperidin-4-yl]-3-(4-trifluoromethoxy-phenyl)ureidomethyl}-benzoylamino}propionic acid methyl ester

To a solution of 3-{4-[1-piperidin-4-yl]-3-(4-trifluoromethoxyphenyl)ureidomethyl}benzoylamino}propionic acid methyl ester hydrochloride (0.20 g) in DMF (5 mL) was added diisopropylethylamine (0.30 mL) and cyclopropylcarboxylic acid chloride (0.16 mL). The mixture was stirred at 25°C overnight. Water (100 mL) and ethyl acetate (100 mL) were added, the phases separated and the organic phase was washed with a solution of NH<sub>4</sub>Cl (sat., 2 x 50 mL) and water (50 mL). Upon drying with MgSO<sub>4</sub> the solvent was evaporated and the residue purified by column chromatography.

3-{4-[1-(1-Cyclopropanecarbonylpiperidin-4-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino}propionic acid

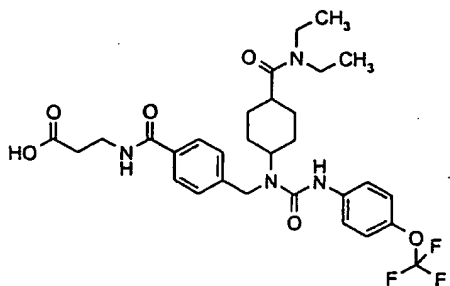
The above 3-{4-[1-(1-cyclopropanecarbonylpiperidin-4-yl)-3-(4-trifluoromethoxyphenyl)-ureidomethyl]benzoylamino}propionic acid methyl ester (0.17 g, 0.28 mmol) was dissolved in 10 mL ethanol and hydrolysed by adding lithium hydroxide (14 mg, 0.56 mmol) dissolved in water (1 mL). The mixture was stirred at 50°C for 2 hours. The solvent was evaporated and water (25 mL) was added to the mixture followed by HCl (1N) adjusting pH to 3-4 allowing the title compound to be isolated as a precipitate.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 12.22 (s br, 1H); 8.60 (s, 1H); 8.45 (t, 1H); 7.75 (d, 2H); 7.55 (d, 2H); 7.32 (d, 2H); 7.22 (d, 2H); 4.62 (s, 2H); 4.50-4.30 (m, 3H); 3.45 (q, 2H); 3.05 (t br, 1H); 2.50 (t, 2H); 1.95 (m, 1H); 1.70-1.40 (m, 4H); 0.70 (m, 4H).

HPLC-MS (method B): *m/z* = 577, *R*<sub>t</sub> = 5.40 min.

EXAMPLE 382

3-{4-[1-(4-Diethylcarbamoylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



4-[(4-Carboxycyclohexylamino)methyl]benzoic acid methyl ester

Methyl 4-formylbenzoate (5 g, 30 mmol) was dissolved in DMF (60 mL) and 4-aminocyclohexylcarboxylic acid (4.36 g, 30 mmol) and NaBH<sub>4</sub> (1.1 g, 30 mmol) were added. The mixture was stirred at 70°C overnight. Trimethylorthoformate (10 mL) was added and the mixture was stirred at 100°C overnight. Toluene was added and the mixture was heated to 135°C and stirred overnight. The solvent was evaporated leaving a DMF solution to which HCl (1N, 30 mL) was added causing precipitation. The desired product was collected by filtration.

4-[1-(4-Carboxycyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid methyl ester

The above 4-[(4-carboxycyclohexylamino)methyl]benzoic acid methyl ester (1g, 3.4 mmol) was dissolved in acetonitrile (25 mL) and 4-trifluoromethoxyphenylisocyanate (0.73 g, 3.4 mmol) was added. Stirring overnight at 50°C followed by cooling to 25°C formed a precipitate, which was removed by filtration. The filtrate was concentrated in vacuo and the product purified by chromatography using silica as stationary phase and a mixture of ethyl acetate, methanol and acetic acid as eluent (15:1:0.1).

4-[1-(4-Diethylcarbamoylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid methyl ester

To the above 4-[1-(4-carboxycyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid methyl ester (0.30 g, 0.6 mmol) dissolved in DMF (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC, 0.12 g, 0.6 mmol) and 1-hydroxybenzotriazole (HOBt, 0.098g, 0.65 mmol). After stirring the mixture 30 min at 25°C, diethylamine (76 µL) was added. The mixture was allowed to react overnight at 25°C. Water (100 mL) and ethyl acetate (100 mL) were added, the phases separated and the aqueous phase was extracted with ethyl acetate (2 x 100 mL). The combined organic phase was dried with MgSO<sub>4</sub> and evaporated to give the desired product.

20

3-{4-[1-(4-Diethylcarbamoylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

The above 4-[1-(4-diethylcarbamoylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid methyl ester was converted into the title compound by methods already described.

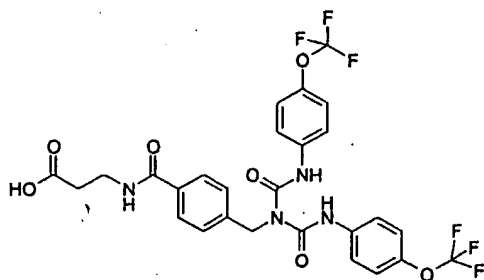
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<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 12.22 (s br, 1H); 8.55 (s, 1H); 8.45 (t, 1H); 7.75 (d, 2H); 7.55 (d, 2H); 7.30 (d, 2H); 7.20 (d, 2H); 4.55 (s, 2H); 4.10 (t br, 1H); 3.45 (q, 2H); 3.20 (m, 2H); 2.70 (s br, 1H); 2.10-1.40 (m, 8H); 1.10 (t, 3H); 0.95 (t, 3H).

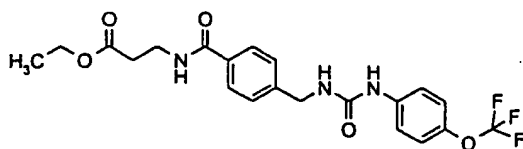
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HPLC-MS (method B): m/z = 607, R<sub>t</sub> = 6.50 min.



EXAMPLE 3833-{4-[1,5-Bis(4-trifluoromethoxyphenyl)-3-biuretmethyl]benzoylamino}propionic acid

- 5 Ethyl 3-(4-aminomethylbenzoylamino)propanoate hydrochloride was prepared from  $\beta$ -alanine ethyl ester hydrochloride and 4-(*tert*-butoxycarbonylaminomethyl)benzoic acid by methods known to those skilled in the art.

3-{4-[3-(4-Trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid ethyl ester

10

- Ethyl 3-(4-Aminomethylbenzoylamino)propanoate hydrochloride (0.25 g, 0.87 mmol) in acetonitrile (5 mL) and diisopropylethylamine (0.15 mL) was allowed to react with 4-trifluoromethoxyphenylisocyanate (0.37 g, 1.74 mmol) at 50°C overnight. Upon cooling to 25°C the product precipitated and was collected by filtration.

15

3-{4-[1,5-Bis(4-trifluoromethoxyphenyl)-3-biuretmethyl]benzoylamino}propionic acid ethyl ester

- To a solution of the above 3-{4-[3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid ethyl ester (0.32 g, 0.71 mmol) in DMF (5 mL) was added sodium hydride (17 mg, 0.71 mmol). The mixture was stirred at 25°C for 1 hr. Then 4-trifluoromethoxyphenylisocyanate (0.22 g, 1.06 mmol) was added and the mixture was stirred 5 hours at 25°C. The product was isolated by filtration.

20

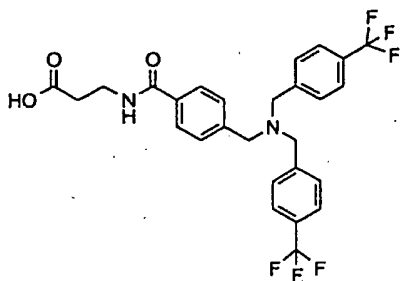
3-{4-[1,5-Bis(4-trifluoromethoxyphenyl)-3-biuret(1-methyl)-benzoylamino]-propionic acid

The above 3-{4-[1,5-bis(4-trifluoromethoxyphenyl)-3-biuret(1-methyl)]benzoylamino}propionic acid ethyl ester was hydrolysed into the title compound by methods already described.

- 5  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  12.22 (s br, 1H); 10.20 (s, 2H); 7.75 (d, 2H); 7.55 (d, 4H); 7.42 (d, 1H); 7.32 (d, 4H); 5.10 (s, 2H); 3.45 (q, 2H).

HPLC-MS (method B):  $m/z$  = 629,  $R_t$  = 7.61 min.

10 EXAMPLE 384

3-(4-([Bis(4-trifluoromethylbenzyl)amino]methyl)benzoylamino)propionic acidResin bound Fmoc  $\beta$ -alanine

- 15 150  $\mu\text{mol}$  Fmoc  $\beta$ -alanine was dissolved in a mixture of 250  $\mu\text{L}$  dichloromethane, 250  $\mu\text{L}$  DMF and 100  $\mu\text{L}$  diisopropylethylamine and added to 50 mg polystyrene resin functionalized with a 2-chlorotrityl chloride linker. After shaking the suspension for 4 hours at 25°C, the resin was isolated by filtration and washed with 2 x 1 mL dichloromethane: methanol:diisopropylethylamine (17:2:1) and 2 x 1 mL DMF.

Resin bound 3-{4-[(9H-fluoren-9-ylmethoxycarbonylamino)methyl]benzoylamino}-propionic acid

To the above resin bound Fmoc  $\beta$ -alanine was added 500  $\mu$ L of a 20% solution of piperidine in DMF. Upon shaking for 30 min, the resin was drained and washed with 1 mL DMF containing 1-hydroxybenzotriazole (50 mg/mL) and DMF (2 x 1 mL). Then 200  $\mu$ mol 4-[(9H-fluoren-9-ylmethoxycarbonylamino)methyl]benzoic acid (74.2 mg) dissolved in a mixture of 430  $\mu$ L DMF and 70  $\mu$ L diethylisopropylamine was added followed by 200  $\mu$ mol bromo-tris-pyrrolidinophosphonium hexafluorophosphate (PyBrOP, 93 mg) dissolved in 500  $\mu$ L DMF. The mixture was shaken for 4 hours at 25°C followed by filtration and washing of the resin with 3 x 1 mL DMF.

Resin bound 3-(4-{[bis(4-trifluoromethylbenzyl)amino]methyl}benzoylamino)propionic acid

The Fmoc protecting group was removed from the above resin bound 3-{4-[(9H-fluoren-9-ylmethoxycarbonylamino)methyl]benzoylamino}propionic acid using 500  $\mu$ L of a 20% solution of piperidine in DMF. Upon shaking for 30 min, the resin was drained and washed with 1 mL DMF containing 1-hydroxybenzotriazole (50 mg/mL) and DMF (2 x 1 mL), 2 x 1 mL 1,2-dichloroethane and 20  $\mu$ L acetic acid dissolved in 1 mL 1,2-dichloroethane.

The resulting resin bound 3-(4-aminomethylbenzoylamino)propionic acid was treated with 98 mg 4-trifluoromethylbenzaldehyde (700  $\mu$ mol) dissolved in 500  $\mu$ L 1,2-dichloroethane, 50  $\mu$ L acetic acid and a slurry of 148 mg NaBH(OAc)<sub>3</sub> (700  $\mu$ mol) in 1 mL 1,2-dichloroethane. Overnight shaking at 25°C followed by filtration and washing with 2 x 1 mL dichloromethane, 2 x 1 mL CH<sub>3</sub>OH:DMF (1:1) and 3 x 1 mL DMF afforded resin bound 3-(4-{[bis(4-trifluoromethylbenzyl)amino]methyl}-benzoylamino)propionic acid.

3-(4-{[Bis(4-trifluoromethylbenzyl)amino]methyl}benzoylamino)propionic acid

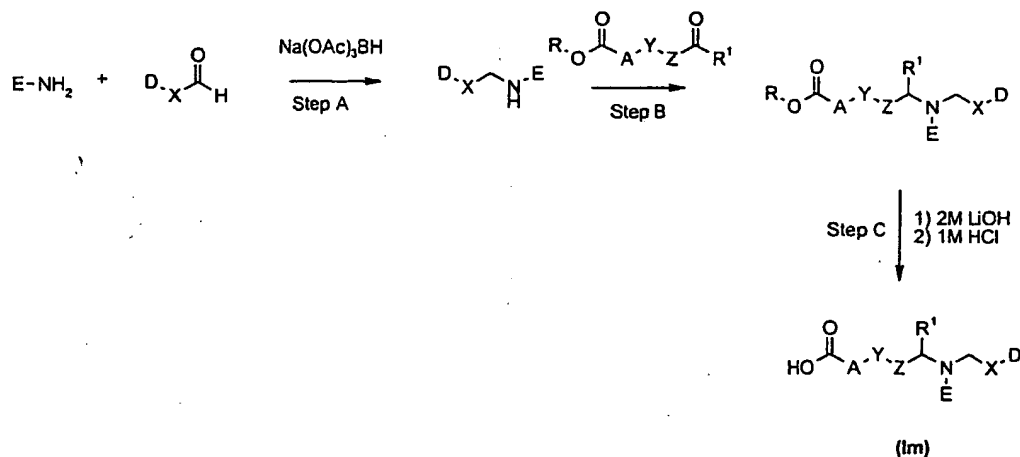
The above resin bound 3-(4-{[bis(4-trifluoromethylbenzyl)amino]methyl}benzoylamino)-propionic acid was treated with 1 mL 5% TFA in dichloromethane for 1 hour at 25°C. The product was filtered off and the resin was washed with 1 mL dichloromethane. The combined extracts were concentrated in vacuo. The residue was dissolved in 50  $\mu$ L DMSO + 500  $\mu$ L CH<sub>3</sub>CN and purified by preparative HPLC using a Supelcosil ABZ+ 25 cm x 10 mm 5 $\mu$  column. The starting eluent composition was 5% CH<sub>3</sub>CN in H<sub>2</sub>O changing over 30 minutes to 90% CH<sub>3</sub>CN in H<sub>2</sub>O which was then kept constant for 5 minutes before going back to the starting composition over 10 min. The flow rate was kept constant at 8 mL/min collecting one fraction per min. The process was monitored using a UV detector operating at 214 nm. The

fractions containing the desired products were combined and evaporated in vacuo to afford the title compound.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.48 (t, 1H); 7.82 (d, 2H); 7.72 (d, 2H); 7.62 (d, 2H); 7.45 (d,  
5 2H); 3.85 (br, 6H).

HPLC-MS (method B): m/z = 539, 5.90 min.

General procedure (N) for the solution phase synthesis of compounds of the general formula (Im):



5 wherein

A, Y, Z, E, X, D and R<sup>1</sup> are as defined for formula (I) and

R is C<sub>1-8</sub>-alkyl.

10

Step A:

The appropriate carbonyl in dichloromethane was reacted with the desired amines (1.1 eq) in dichloromethane. To this solution was added sodium triacetoxymethylborohydride (1.5 eq.) followed by a catalytic amount of acetic acid or TFA. The reaction was left to proceed for 15 hours.

15 The reactions were diluted with ethyl acetate and washed with saturated sodium bicarbonate (2 x), water (2 x), brine, and dried over MgSO<sub>4</sub>. Evaporation of the solvent afforded the crude desired amine.

Step B:

20 To the amine from step A in dichloromethane was added R-OC(O)-A-Y-Z-C(O)-R<sup>1</sup>, eg ethyl 3-[(4-formylbenzoyl)amino]propionate, (0.9 eq) in dichloromethane. R-O(CO)-A-Y-Z-C(O)-R<sup>1</sup> may be prepared in a similar way as described in the general procedure (J) under the general preparation of formylarylcarboxamides. To this solution was added sodium triacetoxymethylborohydride (1.5 eq.) followed by a catalytic amount of acetic acid or TFA. The reaction was  
25 left to proceed for 15 hours. The reactions were diluted with ethyl acetate and washed with

saturated sodium bicarbonate (2 x), water (2 x), brine, and dried over  $\text{MgSO}_4$ . Evaporation of the solvent afforded the crude desired amine.

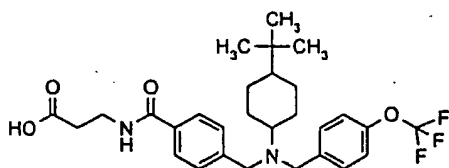
Step C:

- 5 The residue obtained in step B was dissolved in DMF and aqueous 2M lithium hydroxide (10 eq) was added. The reactions were shaken overnight and filtered.

The following examples were prepared according to the general procedure (N).

10 EXAMPLE 385 (general procedure (N))

3-(4-(((4-*tert*-Butylcyclohexyl)-(4-trifluoromethoxybenzyl)amino)methyl)benzoylamino)-propionic acid



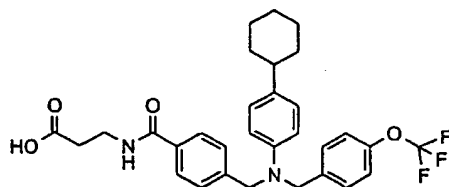
- 15  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  0.79 (s, 9H), 0.86 – 1.05 (m, 3H), 1.60 (qt, 2H), 1.82 (d, 2H), 2.27 (d, 2H), 2.50 (t, 2H), 3.02 (t, 1H), 3.45 (qt, 2H), 4.18 (m, 2H), 4.50 (m, 2H), 7.36 (d, 2H), 7.62 (d, 2H), 7.34 (d, 2H), 7.81 (d, 2H), 8.63 (t, 1H), 10.80 (brd s, 1H), 12.00 (brd s, 1H).

MS (APCI, pos): 535.2, 536.2, 537.2.

20

EXAMPLE 386 (general procedure (N))

3-(4-(((4-Cyclohexylphenyl)-(4-trifluoromethoxybenzyl)amino)methyl)benzoylamino)propionic acid



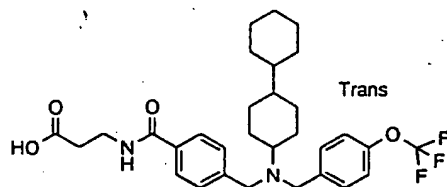
25

$^1\text{H}$  NMR ( $\text{MeOH}-d_4$ ):  $\delta$  0.95 – 1.15 (m, 5H), 1.40 – 1.52 (m, 5H), 2.12 (m, 1H), 2.39 (t, 2H), 3.39 (qt, 2H), 4.47 – 4.49 (m, 4H), 6.51 (d, 2H), 6.77 (d, 2H), 6.91 (d, 2H), 7.06 (m, 4H), 7.50 (d, 2H).

MS (APCI, pos): 552.2

EXAMPLE 387 (general procedure (N))

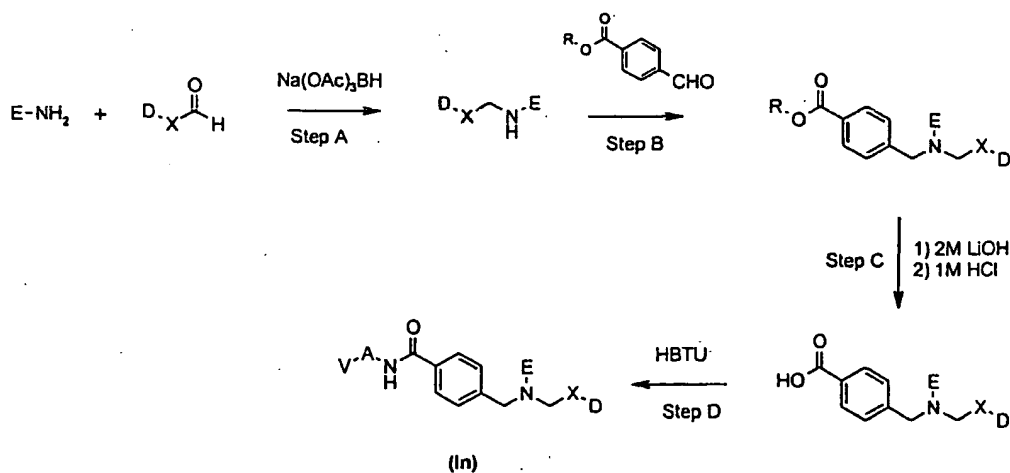
- 5 3-(4-(((trans-4-Cyclohexylcyclohexyl)-(4-trifluoromethoxybenzyl)amino)methyl)benzoyl-  
amino)propionic acid



- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.80 – 1.06 (m, 10H), 1.20 (qt, 2H), 1.51 – 1.90 (m, 9H), 2.14 (t, 2H),  
10 2.20 (m, 1H), 3.33 (t, 2H), 3.57 (brd m, 4H), 7.22 (d, 2H), 7.37 (d, 2H), 7.42 (d, 2H), 7.68 (d, 2H).

MS (APCI, pos): 561.2, 562.2, 489.2.

- 15 General procedure (O) for the solution phase synthesis of compounds of the general formula (In):



- 20 wherein

E, X, D, A, and V are as defined in formula (I), and

R is C<sub>1-8</sub>-alkyl.

Step A:

- 5 The appropriate carbonyl compound, D-X-CHO, in dichloromethane was reacted with the desired amines (1.1 eq) in dichloromethane. To this solution was added sodium triacetoxyborohydride (1.5 eq.) followed by a catalytic amount of acetic acid or TFA. The reaction was left to proceed for 15 hours. The reactions were diluted with ethyl acetate and washed with saturated sodium bicarbonate (2 x), water (2 x), brine, and dried over MgSO<sub>4</sub>. Evaporation of the solvent afforded the crude desired amine.

Step B:

- To the amine from step A in dichloromethane was added C<sub>1-8</sub>-alkyl 4-formylbenzoate (0.9 eq) in dichloromethane. To this solution was added sodium triacetoxyborohydride (1.5 eq.) followed by a catalytic amount of acetic acid or TFA. The reaction was left to proceed for 15 hours. The reactions were diluted with ethyl acetate and washed with saturated sodium bicarbonate (2 x), water (2 x), brine, and dried over MgSO<sub>4</sub>. Evaporation of the solvent afforded the crude desired amine.

20 Step C:

The residue obtained in step B was dissolved in DMF and aqueous 2M lithium hydroxide (10 eq) were added. The reactions were shaken overnight, diluted with ethyl acetate and washed with water (3 x), brine, dried over MgSO<sub>4</sub>, filtered, and concentrated.

25 Step D:

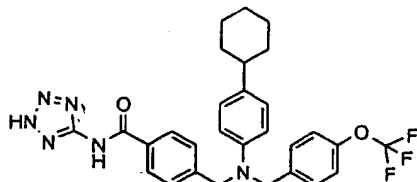
- To a solution of the acid from step C in a suitable solvent such as dichloromethane, DMF, or THF was added diisopropylethylamine (5 eq) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) (1.1 eq). The reaction was allowed to stir for 30 minutes before 5-aminotetrazole hydrochloride (3 eq) was added. The solution was stirred at room temperature for 4 hours. The solvents were evaporated under reduced pressure. The residue was taken up in ethyl acetate and 1 N HCl. The organic layer was separated and washed with H<sub>2</sub>O (2 x), aqueous NaHCO<sub>3</sub> (3 x), brine (2 x), dried over MgSO<sub>4</sub>, and concentrated to give the desired product.

- 35 The following examples were prepared according to the general procedure (O).



EXAMPLE 388 (general procedure (O))

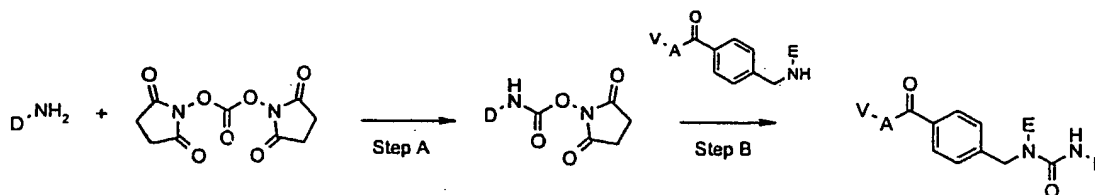
4-[[[(4-Cyclohexylphenyl)-(4-trifluoromethoxybenzyl)amino]methyl]-N-(2H-tetrazol-5-yl)-benzamide



$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.28 (m, 5H), 1.70 (m, 5H), 2.30 (m, 1H), 4.74 (s, 2H), 4.77 (s, 2H), 6.57 (d, 2H), 6.95 (d, 2H), 7.32 – 7.44 (m, 6H), 8.07 (d, 2H), 12.40 (brd s, 1H), 15.90 (brd s, 1H).

MS (APCI, Neg): 549.2, 550.2, 551.2.

General procedure (P) for solution phase synthesis of compounds of the general formula (Io):



wherein

E and D are as defined in formula (I),

A is  $-\text{CH}_2-\text{CH}_2-\text{NH}-$  or  $-\text{NH}-$  and

V is tetrazol-5-yl or  $\text{C}(\text{O})\text{OR}^2$ , wherein  $\text{R}^2$  is hydrogen or  $\text{C}_{1-8}$ -alkyl.

Step A:

The appropriate primary amine (0.011 mmol) in acetonitrile was dispensed into reactor tubes containing *N,N'*-disuccinimidyl carbonate (0.011 mmol) in acetonitrile. The solutions were

stirred at room temperature for 4 hours to give the corresponding carbamates in quantitative yields.

Step B:

- 5 To the resulting carbamates from step A was added the corresponding amine (0.011 mmol) in acetonitrile. The reactions were stirred at 80°C overnight. Evaporation of the solvent under reduced pressure gave the desired urea.

- 10 In case V is C(O)OC<sub>1-6</sub>-alkyl, a third synthesis step C may be added where C(O)OC<sub>1-6</sub>-alkyl is hydrolysed to C(O)OH.

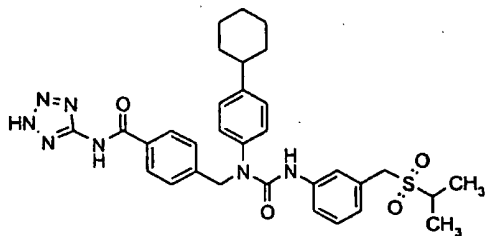
Step C:

- The residue obtained in step B was dissolved in DMF and aqueous 2 M lithium hydroxide (10 eq.) were added into each reaction vessel. The samples were shaken overnight and filtered.
- 15 Aqueous 1 N HCl was then added to give the desired carboxylic acids.

The following examples were prepared according to the general procedure (P).

EXAMPLE 389 (General procedure (P))

- 20 4-{1-(4-Cyclohexylphenyl)-3-[3-(propane-2-sulfonylmethyl)phenyl]ureidomethyl}-N-(2H-tetrazol-5-yl)benzamide



- To a solution of 3-nitrobenzyl bromide (3 g, 13.9 mmol) and 2-propanethiol (1.16 g, 15.3 mmol) in THF (100 mL) was added CsCO<sub>3</sub> (6.5 g, 20 mmol). The mixture was refluxed for 16 hours, and filtered. To the filtrate was added excess 3-chloroperoxybenzoic acid. The mixture was stirred at room temperature for 16 hours, concentrated to one-third volume, diluted with water (100 mL), and extracted with ether. The organic extracts were washed with 10% sodium carbonate, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to provide a mixture containing desired product and starting material. After column chromatography on silicagel, eluting with a mix-
- 25
- 30

ture of hexane and ethyl acetate (2:1) pure isopropyl 3-nitrobenzyl sulfone (2.7 g, 80%) was isolated.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.42 (d, 6H), 3.09 (m, 1H), 4.29 (s, 2H), 7.59 (t, 1H), 7.79 (d, 1H), 8.2-8.3 (s overlap with d, 2H).

To a solution of the above isopropyl 3-nitrobenzyl sulfone (1.4 g, 5.8 mmol) in ethanol (50 mL) was added 100 mg Pd/C(10%). The mixture was stirred under a hydrogen atmosphere at room temperature for 30 min. The catalyst was filtered off, and the filtrate was concentrated to give the isopropyl 3-aminobenzylsulfone.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.32 (d, 6H), 3.02 (m, 1H), 4.15 (s, 2H), 6.65 - 6.82 (m, 3H), 7.14 (t, 1H).

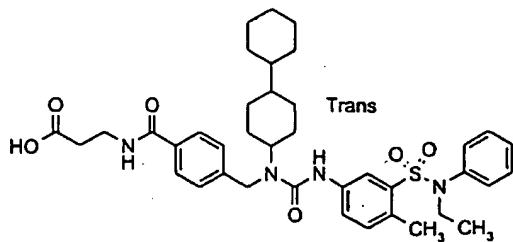
This title compound was prepared from isopropyl 3-aminobenzylsulfone and 4-[(4-cyclohexyl-anilino)methyl]-N-(2H-tetrazol-5-yl)benzamide following the general procedure for formation of ureas with di-(N-succinimidyl)carbonate.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ: 1.27 (d, 6H), 1.28-1.45 (m, 6H), 1.62-1.88 (m, 5H), 3.20 (m, 1H), 4.36 (s, 2H), 4.99 (s, 2H), 7.00 (d, 1H), 7.15-7.30 (m, 3H), 7.47 - 7.55 (m, 4H), 7.98 (d, 2H), 8.28 (s, 1H), 11.3 (br, 1H).

LC-MS (APCI, pos.): 616 (M+1).

#### EXAMPLE 390 (general procedure (P))

3-(4-{1-(*trans*-4-Cyclohexylcyclohexyl)-3-[3-(*N*-ethyl-*N*-phenylsulfamoyl)-4-methylphenyl]-ureidomethyl}benzoylamino)propionic acid

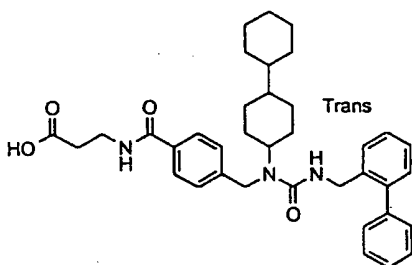


<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.90 - 1.30 (m, 13H), 1.39 (q, 2H), 1.65 (m, 8H), 2.14 (s, 3 H), 2.48 (m, 2H), 3.59 (m, 2H), 3.32 (q, 2H), 4.03 (m, 1H), 4.59 (s, 2H), 7.18 (m, 3H), 7.33 (m, 5H), 7.67 (d, 1H), 7.73 (d, 2H), 7.96 (s, 1H), 8.43 (m, 1H), 8.58 (s, 1 H).

5 MS (APCI, pos.): 703.3 (M+1).

EXAMPLE 391 (general procedure (P))

3-(4-{1-(*trans*-4-Cyclohexylcyclohexyl)-3-biphenyl-2-ylmethyl}ureidomethyl)benzoyl-  
amino)propionic acid



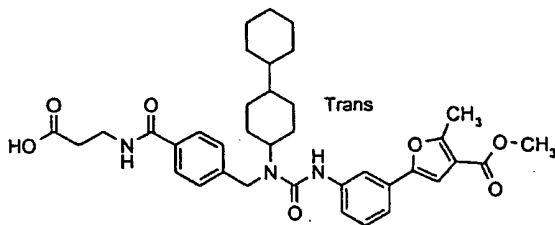
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.62- 1.25 (m, 10H), 1.39 (q, 2H), 1.60 (m, 8H), 2.46 (m, 2 H), 3.43 (q, 2H), 3.85 (m, 1H), 3.97 (d, 2H), 4.44 (s, 2H), 6.50 (s, 1 H), 6.94 (d, 1H), 7.02 -7.23 (m, 10H), 7.52 (d, 2H), 7.75 (d, 2H, 8.23 (t, 1H).

15

MS (APCI, pos.): 596.4 (M+1).

EXAMPLE 392 (general procedure (P))

5-(3-{3-(*trans*-4-Cyclohexylcyclohexyl)-3-[4-(2-carboxyethylcarbamoyl)benzyl]ureido}phenyl)-  
2-methylfuran-3-carboxylic acid methyl ester



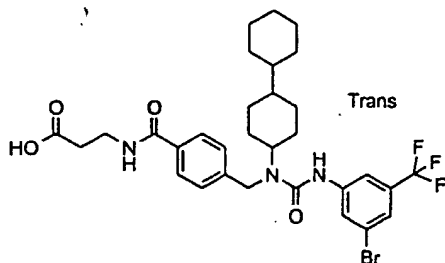
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.70 -1.25 (m, 10H), 1.41 (q, 2H), 1.66 (m, 8H), 2.47 (m, 2H), 3.78 (s, 3H), 4.08 (m, 1H), 4.62 (s, 2H), 7.02 (s, 1H), 7.21- 7.38 (m, 4H), 7.43 (d, 2H), 7.75 (d, 2H), 7.81 (s, 1H), 8.45 (s, 1H).

25

MS (APCI, pos.): 644.3 (M+1).

EXAMPLE 393 (general procedure (P))

- 5 3-{4-[1-(*trans*-4-Cyclohexylcyclohexyl)-3-(3-bromo-5-trifluoromethylphenyl)ureidomethyl]-  
benzoylamino}propionic acid

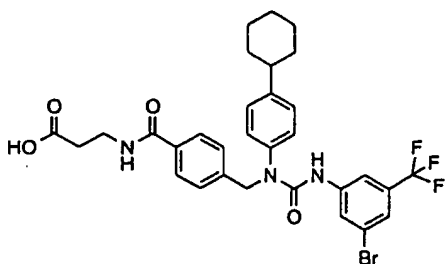


- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.62 - 1.25 (m, 10H), 1.39 (q, 2H), 1.65 (m, 8H), 2.40 (m, 2H), 3.32 (q,  
10 2 H), 4.04 (m, 1H), 4.60 (s, 2H), 7.31 (d, 2H), 7.46 (s, 1H), 7.75 (d, 2H), 7.93 (s, 1H), 8.08 (s,  
1H), 8.45 (s, 1H), 8.83 (s, 1 H).

MS (APCI, pos.): 652.2, 654.1 (M+1).

- 15 EXAMPLE 394 (general procedure (P))

3-{4-[1-(4-Cyclohexylphenyl)-3-(3-bromo-5-trifluoromethylphenyl)ureidomethyl]benzoyl-  
amino}propionic acid

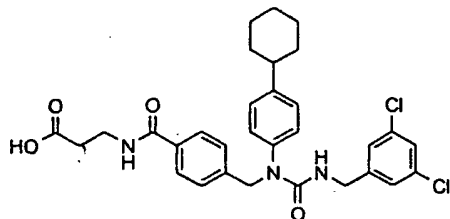


- 20 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.38 (m, 6H), 1.79 (m, 5H), 2.48 (m, 2 H) 4.96 (s, 2H), 7.22 (m, 4H),  
7.36 (d, 2H), 7.50 (s, 1H), 7.77 (d, 2H), 7.94 (s, 1 H), 8.09 (s, 1H), 8.50 (s, 1H), 8.71 (s, 1 H).

MS (APCI, pos.): 646.2, 648.2 (M+1).

**EXAMPLE 395 (general procedure (P))**

3-{4-[1-(4-Cyclohexylphenyl)-3-(3,5-dichlorobenzyl)ureidomethyl]benzoylamino}propionic acid



5

**Step A:**

To a solution of D-NH<sub>2</sub> (eg. 3,5-dichlorobenzylamine) (1.13 mmol) in acetonitrile (10 mL) was added *N,N'*-disuccinimidylcarbonate (360 mg, 1.13 mmol). The reaction mixture was stirred at room temperature for 4 hours.

10

**Step B:**

The intermediate 3-{4-[(4-cyclohexylphenylamino)methyl]benzoylamino} propionic acid ethyl ester (1.13 mmol) and diisopropylethylamine (440 mg, 3.42 mmol) were added to the reaction mixture and the reaction mixture was heated at 75°C overnight and concentrated under reduced pressure. The residue was taken up in ethyl acetate and washed with 1N HCl (2 x), brine (3 x), dried over MgSO<sub>4</sub>, filtered and concentrated. The material was introduced into a silica gel column and eluted with ethyl acetate/hexane (20/80).

15

**Step C:**

The product from step B (150 mg, 0.250 mmol) was dissolved in methanol (20 mL) and 2 M LiOH (20 mL) was added. The reaction was stirred for 30 minutes and concentrated. The residue was introduced into a silica gel column and eluted with ethyl acetate. Recrystallisation from ethyl ether/dichloromethane afforded the title compound as a beige solid (35 mg, 25% yield).

25

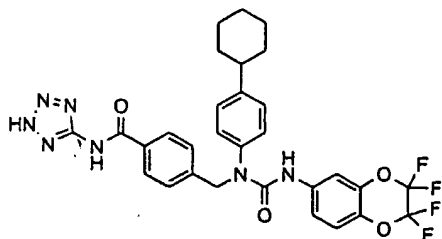
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.10-1.34 (m, 6H), 1.70-1.78 (m, 5H), 2.45 (t, 2H), 3.44 (qt, 2H), 4.21 (d, 2H), 4.84 (s, 2H), 6.55 (t, 1H), 7.08 (d, 2H), 7.19-7.21 (m, 6H), 7.44 (s, 1H), 7.74 (d, 2H), 8.45 (t, 1H), 12.10 (brd s, 1H).

30

MS (APCI, pos): 582.1, 584.2.

**EXAMPLE 396 (general procedure (P))**

4-[1-(4-Cyclohexylphenyl)-3-(2,2,3,3-tetrafluoro-2,3-dihydrobenzo[1,4]dioxin-6-yl)ureido-  
methyl]-N-(2H-tetrazol-5-yl)benzamide



5

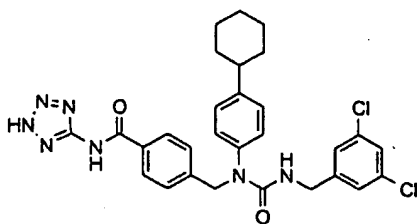
To a solution of 2,2,3,3-tetrafluoro-6-amino-2,3-dihydrobenzo[1,4]dioxine (120 mg, 0.53 mmol) in acetonitrile (10 mL) was added *N,N'*-disuccinimidylcarbonate (130 mg, 0.53 mmol). After stirring the solution for 4 hours at room temperature, 4-[(4-cyclohexylphenylamino)-methyl]-*N*-(1*H*-tetrazol-5-yl)benzamide (200 mg, 0.53 mmol) and diisopropylethylamine (210 mg, 1.59 mmol) were added. The reaction mixture was heated at 75 °C overnight and concentrated under reduced pressure. The residue was taken up in ethyl acetate and washed with 1N HCl (2 x), brine (3 x), dried over MgSO<sub>4</sub>, filtered and concentrated. The material was introduced into a silica gel column and eluted with MeOH/ethyl acetate (5/95). The crude product was then recrystallized from ethyl acetate/hexane to afford the title compound as a white-beige powder (12 mg, 0.019 mmol).

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.36 (m, 6H), 1.78 (m, 5H), 4.99 (s, 2H), 7.21 (m, 4H), 7.33 (s, 2H), 7.45 (d, 2H), 7.63 (s, 1H), 8.01 (s, 2H), 8.57 (s, 1H), 12.20 (brd s, 1H), 16.00 (brd s, 1H).

20 MS (APCI, pos): 626.2, 627.2.

**EXAMPLE 397 (general procedure (P))**

**4-[1-(4-Cyclohexylphenyl)-3-(3,5-dichlorobenzyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide**



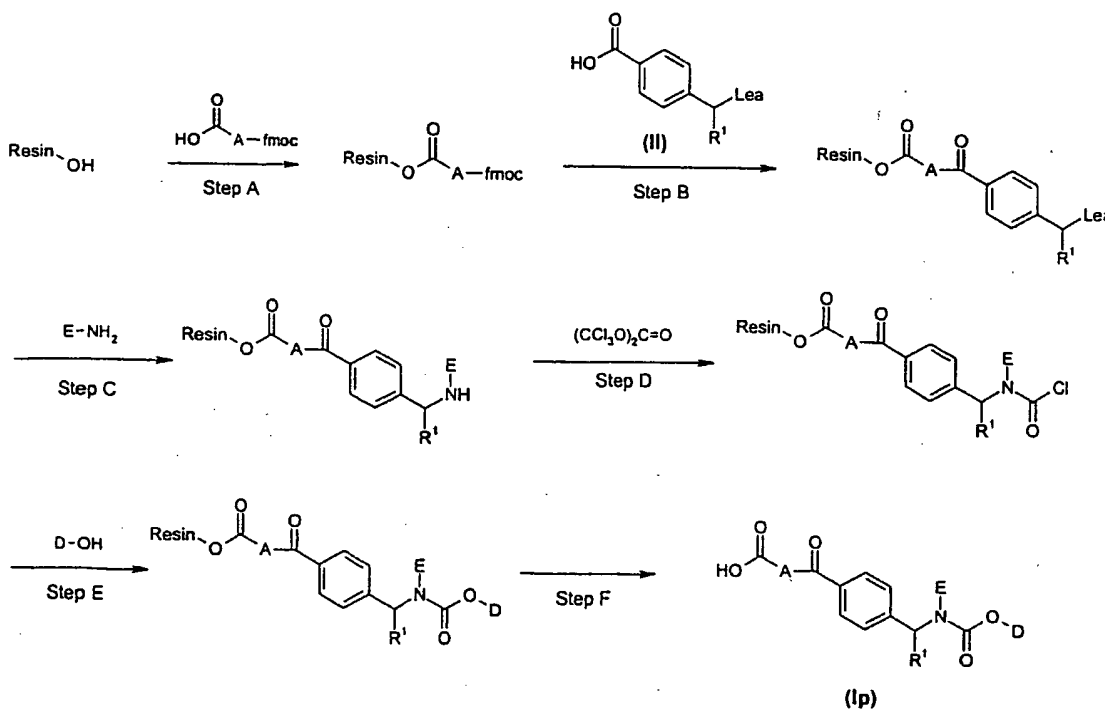
25

To a solution of 3,5-dichlorobenzylamine (200 mg, 1.14 mmol) was added *N,N'*-disuccinimidylcarbonate (360 mg, 1.13 mmol). After stirring the solution for 4 hours at room temperature, tetrazolylaminoamidobenzylaniline (420 mg, 1.13 mmol) and diisopropylethylamine (440 mg, 3.42 mmol) were added. The reaction was heated at 75 °C overnight and concentrated under reduced pressure. The residue was taken up in ethyl acetate and washed with 1N HCl (2 x), brine (3 x), dried over MgSO<sub>4</sub>, filtered and concentrated. The title compound was purified by preparatory HPLC.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 11.22 (m, 6H), 1.71 (m, 5H), 4.24 (s, 2H), 4.90 (s, 2H), 6.64 (t, 1H), 7.13 (d, 2H), 7.23 (d, 2H), 7.27 (s, 2H), 7.39 (d, 2H), 7.45 (s, 1H), 8.04 (d, 2H), 12.29 (brd s, 1H), 16.00 (brd s, 1H).

MS (APCI, pos): 580.0.

15 General procedure (Q) for the solid phase synthesis of compounds of the general formula (Ip):



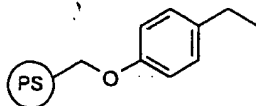
20 wherein



A, R<sup>1</sup>, E and D are as defined for formula (Ia),

Lea is a leaving group such as chloro, bromo, iodo, mesyl or tosyl, and

- 5 Resin denotes a polystyrene resin with a linker such as the Wang linker:



wherein PS denotes polystyrene.

10

Step A, Step B and Step C are performed as described under general procedure (A).

Alternatively, the resin can be a polystyrene resin with a 2-chlorotrityl linker. In this case, step A is performed as described in eg general procedure (L) or general procedure (V).

15

Step D:

The reaction is performed by stirring resin bound intermediate obtained as described in step C with bistrichloromethyl carbonate (3.3 equivalents). The reaction is carried out in solvents such as dichloromethane, 1,2-dichloroethane or toluene, containing 10 equivalents of a base such as diisopropylethylamine, triethylamine, dicyclohexylamine and the like. The reaction is performed between 0°C and 40°C, preferably between 0°C and 20°C. When the reaction is complete (1-3 h), excess of reagent is removed by filtration. The resin is then washed with dichloromethane and dried in vacuo to leave the resin bound chlorocarbamoyl derivatized intermediate.

25

Step E:

The reaction is performed by stirring resin bound chlorocarbamoyl derivatized intermediate as obtained in step D, with a 10-20 molar excess of alcohols of the type D-OH in the presence of an equal molar excess of base such as diisopropylethylamine, triethylamine, dicyclohexylamine, diazabicycloundecene, or preferably [2.2.2]-diazabicyclooctane. The reaction is carried out in solvents such as DMF, N-methyl-2-pyrrolidone, dichloromethane, 1,2-dichloroethane, THF, toluene or mixtures of one or more of these. The reaction is performed between 0°C and 120°C, preferably at 25°C. When the reaction is completed (12-16 hours) ex-

30

cess of reagent is removed by filtration. The resin is then washed with the solvent used during the reaction followed by several washes with dichloromethane. The resin is dried in vacuo to leave the resin bound carbamate.

5 Step F:

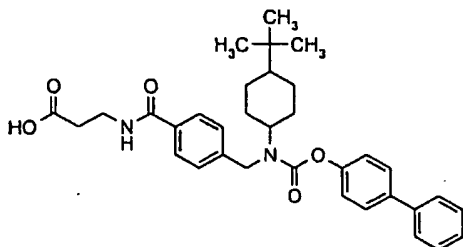
The reaction is known (The combinatorial Index, Ed. Bunin, B.A. 1998, Academic Press, p. 21) and is generally performed by stirring resin bound intermediate with a 5-95% solution of TFA in dichloromethane. The reaction is performed between 0°C and 40°C, preferably at 25°C. When the reaction is complete, the product is removed by filtration. The resin is successively washed with the solvent used during the reaction, optionally containing TFA. The  
10 product and the washings are collected, and the solvent is removed in vacuo.

Specific examples illustrating the preparation of compounds of the general formula (Ip) according to the invention are provided below.

15

EXAMPLE 398 (general procedure (Q))

3-(4-[(Biphenyl-4-yloxy-carbonyl)-(4-*tert*-butylcyclohexyl)amino]methyl)benzoylamino)-propionic acid



20

Step D: Resin bound 3-{4-[1-(4-*tert*-butylcyclohexyl)-*N*-(chlorocarbamoyl)aminomethyl]-benzoylamino}propionic acid

Resin bound 3-{4-[1-(4-*tert*-butylcyclohexyl)aminomethyl]benzoylamino}propionic acid (100 mg, 0.1 mmol) as prepared according to step C under general procedure A was suspended in dichloromethane for 1 hour. Solvent was removed by filtration, and a mixture of bistrichloromethyl carbonate (89 mg, 0.3 mmol) and diisopropylethylamine (175  $\mu$ l, 1.0 mmol) in dichloromethane (1.0 mL) was added. The mixture was stirred for 90 min. at room temperature. Excess of reagents were removed by filtration, and the resin was subsequently washed with dichloromethane (4 x). The resin was dried in vacuo to leave 105 mg of resin bound  
25

3-{4-[1-(4-*tert*-butylcyclohexyl)-*N*-(chlorocarbamoyl)aminomethyl]benzoylamino}propionic acid.

Step E: Resin bound 3-(4-[[biphenyl-4-yloxy-carbonyl)-(4-*tert*-butylcyclohexyl)amino]methyl]-benzoylamino)propionic acid

To the resin (50 mg, 0.05 mmol) prepared in step D was added a solution of (85 mg; 0.5 mmol) biphenyl-4-ol, and (2.2.2)-diazabicyclooctane (56 mg; 0.5 mmol) in DMF (1.0 mL). The mixture was stirred at room temperature overnight. Solvent was removed, and the resin was washed with DMF (3 x) followed by dichloromethane (10 x). The resin was dried *in vacuo* to leave 65 mg of resin bound 3-(4-[[biphenyl-4-yloxy-carbonyl)-(4-*tert*-butylcyclohexyl)amino]-methyl]benzoylamino)propionic acid

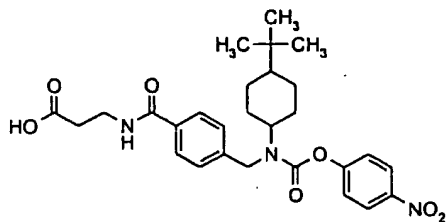
Step F: 3-(4-[[Biphenyl-4-yloxy-carbonyl)-(4-*tert*-butylcyclohexyl)amino]methyl]-benzoylamino)propionic acid

To the resin obtained above was added 2 mL of 50% of TFA in dichloromethane. After stirring for 30 min. at 25°C, the solvent was removed by filtration. The resin was washed twice with 50% of TFA in dichloromethane, and the combined filtrate and washings were evaporated to dryness by speed vacuum centrifugation, to leave the title material as a light coloured oil. The product was characterised by analytical HPLC-MS and NMR.

<sup>1</sup>H NMR (DMSO): δ 8.44 (s, 1H); 8.35 (s, 1H); 7.78 (d, 2H); 7.45 (d, 2H); 7.38 (d, 2H); 7.34 (d, 2H); 6.94 (m, 5H); 4.60 (s, 2H); 0.81 (s, 9H).

EXAMPLE 399 (general procedure (Q))

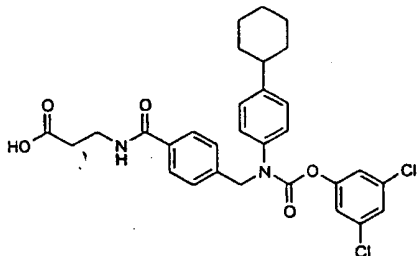
3-(4-[[4-*tert*-Butylcyclohexyl)-(4-nitrophenoxy-carbonyl)amino]methyl]benzoylamino)propionic acid



<sup>1</sup>H NMR (DMSO): δ 8.40 (t, 1H); 8.25 (d, 2H); 7.82 (d, 2H); 7.78 (d, 2H); 7.44 (d, 2H); 4.61 (s, 2H); 0.85 (s, 9H).

EXAMPLE 400 (general procedure (Q))

3-(4-(((4-Cyclohexylphenyl)-(3,5-dichlorophenoxy)carbonyl)amino)methyl)benzoylamino)-propionic acid

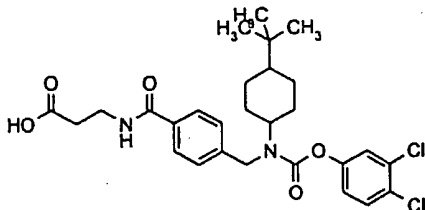


5

$^1\text{H}$  NMR (DMSO):  $\delta$  8.57 (t, 1H); 7.88 (d, 2H); 7.60 (s, 1H); 7.50 (m, 4H); 7.40 (d, 2H); 7.29 (d, 2H).

EXAMPLE 401 (general procedure (Q))

10 3-(4-(((4-*tert*-Butylcyclohexyl)-(3,4-dichlorophenoxy)carbonyl)amino)methyl)benzoylamino)-propionic acid

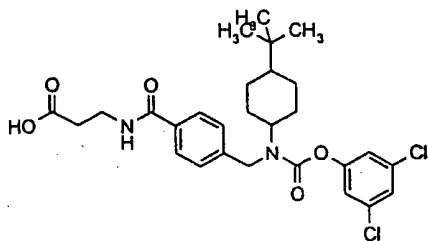


15

$^1\text{H}$  NMR (DMSO):  $\delta$  8.58 (t, 1H); 7.91 (d, 2H); 7.73 (d, 1H); 7.58 (d, 1H); 7.48 (d, 2H); 7.22 (d, 1H).

EXAMPLE 402 (general procedure (Q))

3-(4-(((4-*tert*-Butylcyclohexyl)-(3,5-dichlorophenoxy)carbonyl)amino)methyl)benzoylamino)-propionic acid

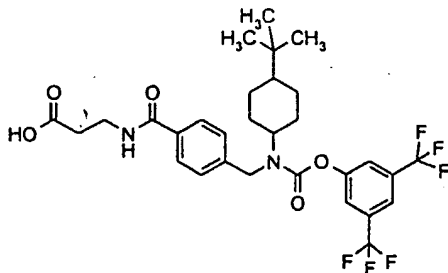


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$^1\text{H}$  NMR (DMSO):  $\delta$  8.59 (t, 1H); 7.90 (d, 2H); 7.55 (m, 4H); 7.35 (s, 1H).

EXAMPLE 403 (general procedure (Q))

3-(4-(((3,5-Bis(trifluoromethyl)phenoxy)carbonyl)-(4-*tert*-butylcyclohexyl)amino)methyl)-benzoylamino)propionic acid

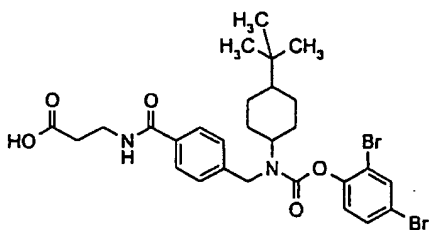


5

<sup>1</sup>H NMR (DMSO): δ 8.58 (t, 1H); 8.12 ((d, 1H); 8.05 (d, 2H); 7.90 (m, 2H); 7.55 (m, 2H).

EXAMPLE 404 (general procedure (Q))

10 3-(4-(((4-*tert*-Butylcyclohexyl)-(2,4-dibromophenoxy)carbonyl)amino)methyl)benzoylamino)-propionic acid

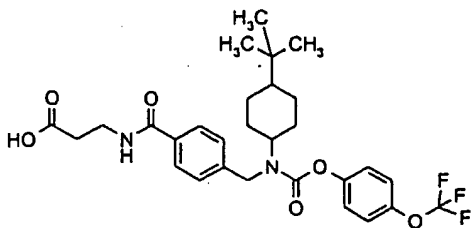


<sup>1</sup>H NMR (DMSO): δ 8.04 (s, 1H); 7.91 (d, 2H); 7.71 (d, 1H); 7.52 (d, 2H); 7.37 (m, 1H).

15

EXAMPLE 405 (general procedure (Q))

3-(4-(((4-*tert*-Butylcyclohexyl)-(4-trifluoromethoxyphenoxy)carbonyl)amino)methyl)benzoyl-amino)propionic acid

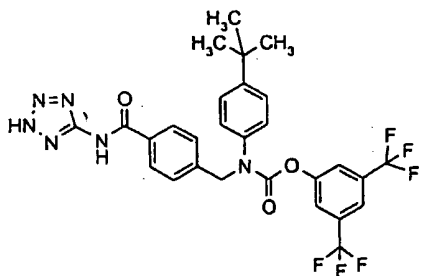


20

<sup>1</sup>H NMR (DMSO): δ 8.59 (t, 1H); 7.91 (d, 2H); 7.47 (dd, 4H); 7.30 (d, 2H).

EXAMPLE 406 (general procedure (Q))

(4-*tert*-Butylphenyl)-[4-(2H-tetrazol-5-ylcarbamoyl)benzyl]carbamic acid 3,5-bis(trifluoromethyl)phenyl ester

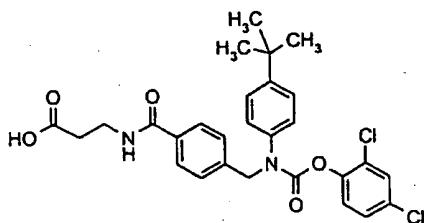


5

<sup>1</sup>H NMR (DMSO): δ 8.17 (s, 2H); 8.11 (s, 1H); 7.67 (d, 2H); 7.51 (m, 4H); 5.18 (s, 2H).

EXAMPLE 407 (general procedure (Q))

10 3-(4-[(4-*tert*-Butylphenyl)-(2,4-dichlorophenoxy)carbonyl]amino)methyl)benzoylamino)-propionic acid

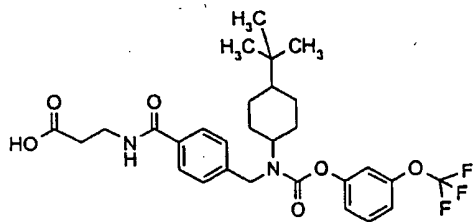


15

<sup>1</sup>H NMR (DMSO): δ 8.58 (t, 1H); 7.89 (d, 2H); 7.84 (s, 1H); 7.56 (dd, 1H); 7.48 (m, 5H); 7.39 (d, 2H); 5.06 (s, 2H).

EXAMPLE 408 (general procedure (Q))

3-(4-[(4-*tert*-Butylcyclohexyl)-(3-trifluoromethoxyphenoxy)carbonyl]amino)methyl)benzoylamino)propionic acid

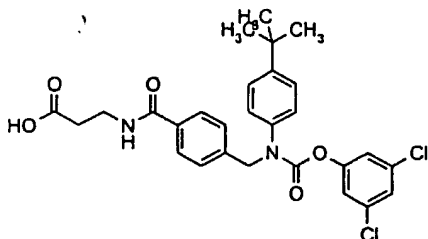


20

<sup>1</sup>H NMR (DMSO): δ 8.59 (t, 1H); 7.91 (d, 2H); 7.69 (t, 1H); 7.47 (dd, 4H); 7.32 (m, 1H); 7.27 (m, 1H); 7.20 (m, 1H).

EXAMPLE 409 (general procedure (Q))

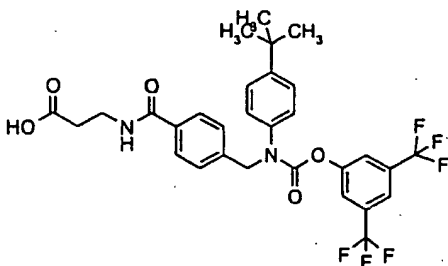
- 5 3-(4-(((4-*tert*-Butylphenyl)-(3,5-dichlorophenoxy)carbonyl)amino)methyl)benzoylamino)-propionic acid



- 10 <sup>1</sup>H NMR (DMSO): δ 8.60 (t, 1H); 7.88 (d, 2H); 7.60 (s, 1H); 7.50 (m, 4H); 7.46 (d, 2H); 7.43 (d, 2H); 5.08 (s, 2H).

EXAMPLE 410 (general procedure (Q))

- 3-(4-(((3,5-Bis(trifluoromethyl)phenoxy)carbonyl)-(4-*tert*-butylphenyl)amino)methyl)benzoylamino)propionic acid

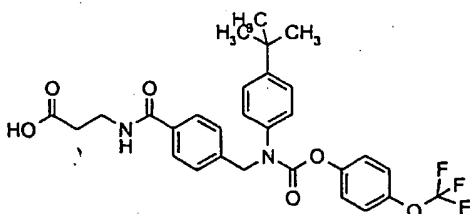


15

<sup>1</sup>H NMR (DMSO): δ 8.60 (t, 1H); 8.15 (s, 2H); 8.10 (s, 1H); 7.89 (d, 2H); 7.55 (d, 2H); 7.49 (s, 4H); 5.11 (s, 1H).

**EXAMPLE 411 (general procedure (Q))**

3-(4-((4-*tert*-Butylphenyl)-(4-trifluoromethoxyphenoxy)carbonyl)amino)methyl)benzoylamino)-propionic acid

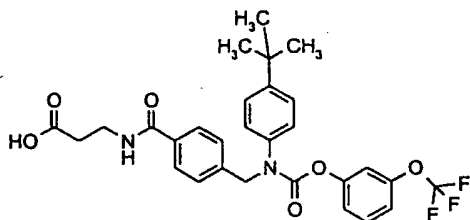


5

<sup>1</sup>H NMR (DMSO): δ 8.59 (t, 1H); 7.88 (d, 2H); 7.48 (m, 6H); 7.39 (m, 4H); 5.09 (s, 2H).

**EXAMPLE 412 (general procedure (Q))**

3-(4-((4-*tert*-Butylphenyl)-(3-trifluoromethoxyphenoxy)carbonyl)amino)methyl)benzoylamino)-propionic acid



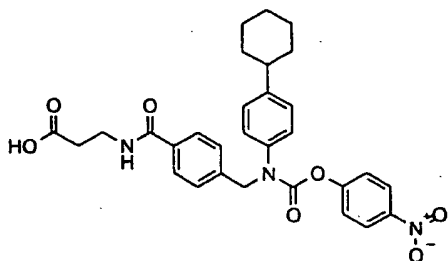
10

<sup>1</sup>H NMR (DMSO): δ 8.59 (t, 1H); 7.88 (d, 2H); 7.61 (t, 1H); 7.48 (m, 4H); 7.39 (m, 5H); 5.09 (s, 2H).

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**EXAMPLE 413 (general procedure (Q))**

3-(4-((4-Cyclohexylphenyl)-(4-nitrophenoxy)carbonyl)amino)methyl)benzoylamino)propionic acid



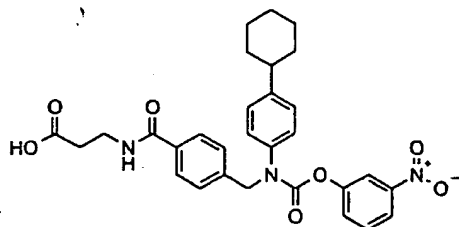
20



<sup>1</sup>H NMR (DMSO): δ 8.57 (t, 1H); 8.36 (d, 2H); 7.88 (d, 2H); 7.55 (d, 2H); 7.49 (d, 2H); 7.40 (d, 2H); 7.31 (d, 2H); 5.09 (s, 2H).

EXAMPLE 414 (general procedure (Q))

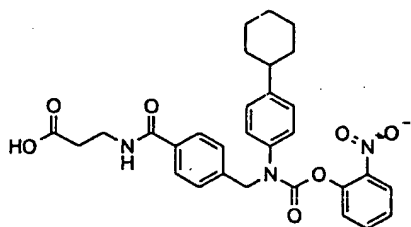
5 3-(4-[[[(4-Cyclohexyl)phenyl]-(3-nitrophenoxy)carbonyl]amino]methyl]benzoylamino)propionic acid



10 <sup>1</sup>H NMR (DMSO): δ 8.57 (t, 1H); 8.19 (m, 2H); 7.88 (d, 2H); 7.76 (dd, 2H); 7.51 (d, 2H); 7.41 (d, 2H); 7.31 (d, 2H); 5.10 (s, 2H).

EXAMPLE 415 (general procedure (Q))

3-(4-[[[(4-Cyclohexyl)phenyl]-(2-nitrophenoxy)carbonyl]amino]methyl]benzoylamino)propionic acid

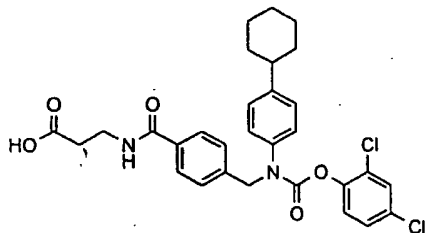


15

<sup>1</sup>H NMR (DMSO): δ 8.59 (t, 1H); 8.21 (d, 1H); 7.89 (m, 3H); 7.63-7.31 (m, 7H); 5.05 (s, 2H).

**EXAMPLE 416 (general procedure (Q))**

3-(4-((4-Cyclohexylphenyl)-(2,4-dichlorophenoxy)carbonyl)amino)methyl)benzoylamino)-propionic acid

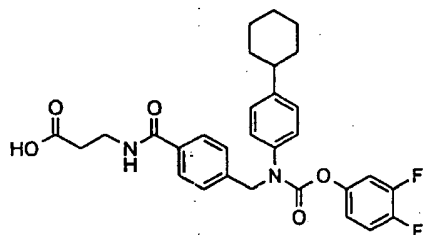


5

<sup>1</sup>H NMR (DMSO): δ 8.58 (t, 1H); 7.88 (d, 2H); 7.83 (s, 1H); 7.57-7.45 (m, 5H); 7.38 (d, 2H); 7.31 (d, 2H); 5.06 (s, 2H).

**EXAMPLE 417 (general procedure (Q))**

10 3-(4-((4-Cyclohexylphenyl)-(3,4-difluorophenoxy)carbonyl)amino)methyl)benzoylamino)-propionic acid

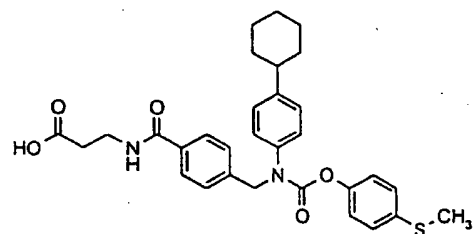


15

<sup>1</sup>H NMR (DMSO): δ 8.58 (t, 1H); 7.87 (d, 2H); 7.55-7.45 (m, 4H); 7.38 (d, 2H); 7.29 (d, 2H); 7.13 (m, 1H); 5.07 (s, 2H).

**EXAMPLE 418 (general procedure (Q))**

3-(4-((4-Cyclohexylphenyl)-(4-methylsulfanylphenoxy)carbonyl)amino)methyl)benzoylamino)-propionic acid

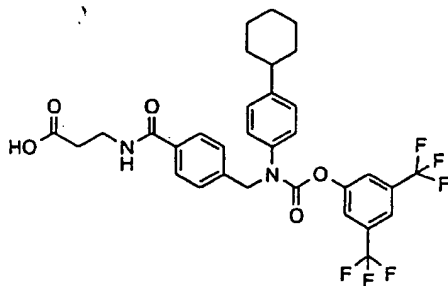


20

<sup>1</sup>H NMR (DMSO): δ 8.58 (t, 1H); 7.87 (d, 2H); 7.46 (d, 2H); 7.35 (m, 4H); 7.29 (d, 2H); 7.18 (d, 2H); 5.07 (s, 2H).

EXAMPLE 419 (general procedure (Q))

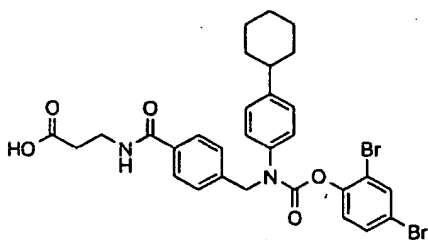
- 5 3-(4-((3,5-Bis(trifluoromethyl)phenoxy)carbonyl)-(4-cyclohexylphenyl)amino)methyl)-benzoylamino)propionic acid



- 10 <sup>1</sup>H NMR (DMSO): δ 8.58 (t, 1H); 8.14 (s, 2H); 8.10 (s, 1H); 7.88 (d, 2H); 7.53 (d, 2H); 7.47 (d, 2H); 7.31 (d, 2H); 5.10 (s, 2H).

EXAMPLE 420 (general procedure (Q))

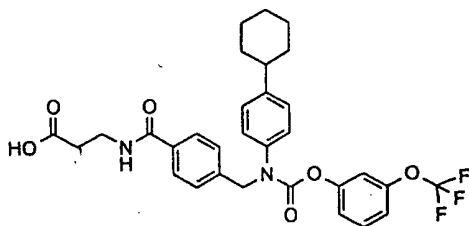
- 15 3-(4-((4-Cyclohexylphenyl)-(2,4-dibromophenoxy)carbonyl)amino)methyl)benzoylamino)-propionic acid



<sup>1</sup>H NMR (DMSO): δ 8.57 (t, 1H); 8.04 (s, 1H); 7.88 (d, 2H); 7.72 (d, 1H); 7.50 (bd, 2H); 7.42 (m, 3H); 7.38 (d, 2H); 5.05 (s, 2H).

**EXAMPLE 421 (general procedure (Q))**

3-(4-((4-Cyclohexylphenyl)-(3-trifluoromethoxyphenoxycarbonyl)amino)methyl)benzoyl-amino)propionic acid

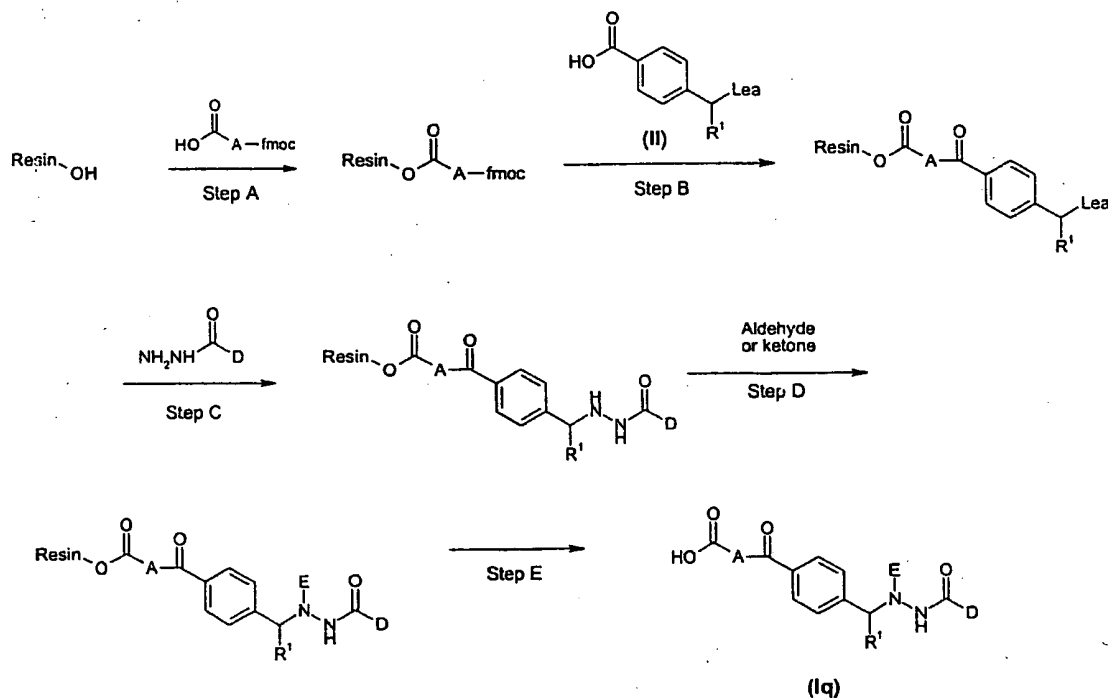


5

<sup>1</sup>H NMR (DMSO): δ 8.59 (t, 1H); 7.88 (d, 2H); 7.62 (t, 1H); 7.49 (d, 2H); 7.41-7.30 (m, 7H); 5.09 (s, 2H).

General procedure (R) for the solid phase synthesis of compounds of the general formula

10 (Iq):



wherein

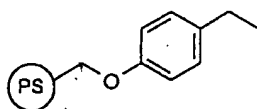
15

A, R<sup>1</sup>, E and D are as defined for formula (Ia).

Lea is a leaving group such as chloro, bromo, iodo, mesyl or tosyl, and

Resin denotes a polystyrene resin with a linker such as the Wang linker:

5



wherein PS denotes polystyrene.

10 Step A and Step B are performed as described under general procedure A.

Step C:

The reaction is performed by stirring the resin bound intermediate obtained in step B with 10 - 20 molar excess of hydrazide. The nucleophilic displacement is carried out in solvents such as DMSO, DMF, *N*-methyl-2-pyrrolidone or mixtures of two or more of these. The reaction is performed between 20°C and 120°C, preferably between 60°C and 80°C. When the reaction is complete, excess of reagent is removed by filtration. The resin is successively washed with the solvent used in the reaction, followed by washings with methanol. The resin bound product can be further dried and analyzed.

20

Step D:

The reductive amination is generally known (The combinatorial Index, Ed. Bunin, B.A. 1998, Academic Press, p. 167) and is performed by stirring the resin bound hydrazide intermediate obtained in step C with an excess of aldehyde or ketone at low pH (by addition of an acid, such as acetic or formic acid). The reaction is carried out in solvents such as THF, DMF, *N*-methyl-2-pyrrolidone, ethanol, methanol, dichloromethane, 1,2-dichloroethane, trimethyl orthoformate, triethyl orthoformate, or mixtures of two or more of these. As reducing reagent sodium cyanoborohydride can be used. The reaction is performed between 20°C and 120°C, preferably at 25°C. When the reaction is complete, excess of reagents are removed by filtration and the resin is washed several times with the solvent used during the reaction. The resin bound product can be further dried and analyzed.

30

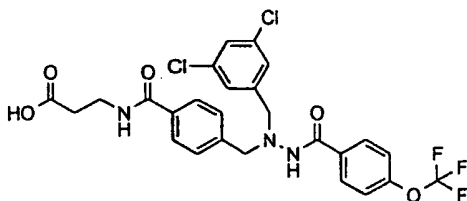
Step E:

The cleavage reaction is known (The combinatorial Index, Ed. Bunin, B.A. 1998, Academic Press, p. 21) and is generally performed by stirring resin bound intermediate with a 5-95% solution of TFA in dichloromethane. The reaction is performed between 0°C and 40°C, preferably at 25°C. When the reaction is complete, the product is removed by filtration. The resin is successively washed with the solvent used during the reaction, optionally containing TFA. The product and the washings are collected, and solvent removed in vacuo.

Specific examples illustrating the preparation of compounds of the general formula (Iq) according to the invention are provided below.

EXAMPLE 422 (general procedure (R))

3-{4-[N-(3,5-Dichlorobenzyl)-N'-(4-trifluoromethoxybenzoyl)hydrazinomethyl]benzoylamino}-propionic acid



Step C: Resin bound 3-{4-[N'-(4-trifluoromethoxybenzoyl)hydrazinomethyl]benzoylamino}-propionic acid

Resin bound 3-[4-(bromomethyl)benzoylamino]propionic acid (50 mg; 0.05 mmol) prepared as described under general procedure (A), was suspended in DMSO for an hour. Solvent was removed by filtration, and a solution of 4-trifluoromethoxybenzoylhydrazide (110 mg; 0.5 mmol) in DMSO (1 mL) was added. The reaction mixture was stirred at 80°C for 16 hours, before removing excess of reagent by filtration. The resin was then washed with DMF (3 x 1 mL) followed by dichloromethane (3 x 1 mL) to afford 50 mg of resin bounded 3-{4-[N'-(4-trifluoromethoxybenzoyl)hydrazinomethyl]benzoylamino}propionic acid.

Step D: Resin bound 3-{4-[N-(3,5-Dichlorobenzyl)-N'-(4-trifluoromethoxybenzoyl)hydrazinomethyl]benzoylamino}propionic acid

To resin bound intermediate obtained as above was added a mixture of 3,5-dichloro-benzaldehyde (175 mg, 1.0 mmol) and acetic acid (0.1 mL) in trimethyl orthoformate (1.0 mL). The resin was stirred for 2 h at ambient temperature. Sodium cyanoborohydride (63 mg, 1.0

mmol) dissolved in DMF (1.0 mL) was then added and the mixture was left stirred at room temperature for 16 h. Excess of reagent was removed by filtration, and the resin was washed with DMF (3 x 1 mL) followed by dichloromethane (8 x).

5 Step E: 3-{4-[N-(3,5-Dichlorobenzyl)-N'-(4-trifluoromethoxybenzoyl)hydrazinomethyl]-benzoylamino}propionic acid

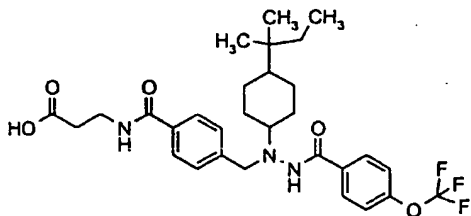
To the resin obtained above was added 2 mL of 50% of TFA in dichloromethane. After stirring for 30 min. at 25°C, the solvent was removed by filtration. The resin was washed twice with 50% of TFA in dichloromethane, and the combined filtrate and washings were taken to dryness by speed vacuum centrifugation, to leave the title compound as a light coloured oil. The product was characterised by analytical LC-MS and NMR.

<sup>1</sup>H NMR (DMSO): δ 9.62 (s, 1H); 8.47 (t, 1H); 7.80 (d, 2H); 7.70 (d, 2H); 7.52 (s, 2H); 7.49 (d, 2H); 7.42 (d, 2H); 4.22 (s, 2H); 4.16 (s, 2H).

HPLC-MS (Method B): m/z = 584.2 (M+1). R<sub>t</sub> = 7.11 min.

EXAMPLE 423 (general procedure (R))

20 3-{4-[N-[4-(1,1-Dimethylpropyl)cyclohexyl]-N'-(4-trifluoromethoxybenzoyl)hydrazinomethyl]-benzoylamino}propionic acid

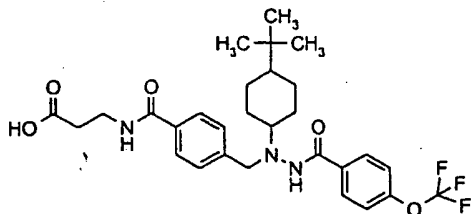


<sup>1</sup>H NMR (DMSO): δ 9.21 (s, 1H); 8.42 (s, 1H); 7.73 (dd, 4H); 7.49 (d, 2H); 7.40 (d, 2H); 4.11 (s, 2H); 1.20 (t, 3H); 1.04 (q, 2H); 0.74 (s, 6H).

HPLC-MS (Method B): m/z = 578.2 (M+1). R<sub>t</sub> = 7.74 min.

**EXAMPLE 424 (general procedure (R))**

3-{4-[N-(4-*tert*-Butylcyclohexyl)-N'-(4-trifluoromethoxybenzoyl)hydrazinomethyl]benzoyl-amino}propionic acid



5

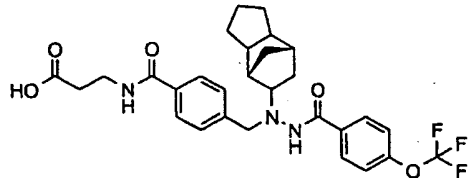
$^1\text{H}$  NMR (DMSO):  $\delta$  9.20 (s, 1H); 8.42 (t, 1H); 7.72 (dd, 4H); 7.50 (d, 2H); 7.40 (d, 2H); 4.14 (s, 2H); 0.84 (s, 9H).

HPLC-MS (Method B):  $m/z$  = 564.4 (M+1).  $R_t$  = 7.47 min.

10

**EXAMPLE 425 (general procedure (R))**

3-{4-[N-(Octahydro-4,7-methanoinden-5-yl)-N'-(4-trifluoromethoxybenzoyl)hydrazinomethyl]-benzoylamino}propionic acid



15

$^1\text{H}$  NMR (DMSO):  $\delta$  9.29 (s, 1H); 8.46 (t, 1H); 7.75 (d, 2H); 7.70 (d, 2H); 7.47 (d, 2H); 7.40 (d, 2H).

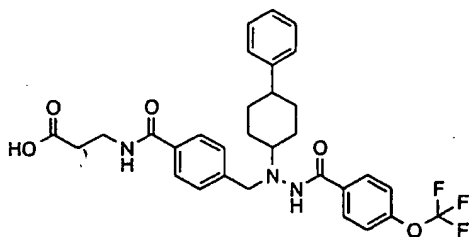
HPLC-MS (Method B):  $m/z$  = 560.4 (M+1).  $R_t$  = 7.51 min.

20



EXAMPLE 426 (general procedure (R))

3-{4-[N-(4-Phenylcyclohexyl)-N'-(4-trifluoromethoxybenzoyl)hydrazinomethyl]benzoylamino}-propionic acid



5

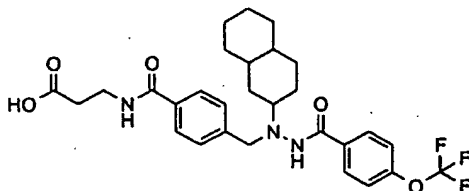
$^1\text{H}$  NMR (DMSO):  $\delta$  9.38 (s, 1H); 8.46 (t, 1H); 7.76 (d, 2H); 7.71 (d, 2H); 7.53 (d, 2H); 7.40 (d, 2H); 7.18-7.43 (m, 5H); 4.18 (s, 2H).

HPLC-MS (Method B):  $m/z$  = 584.4 ( $M+1$ ).  $R_t$  = 7.01 min.

10

EXAMPLE 427 (general procedure (R))

3-{4-[N-(Decahydronaphthalen-2-yl)-N'-(4-trifluoromethoxybenzoyl)hydrazinomethyl]benzoylamino}propionic acid



15

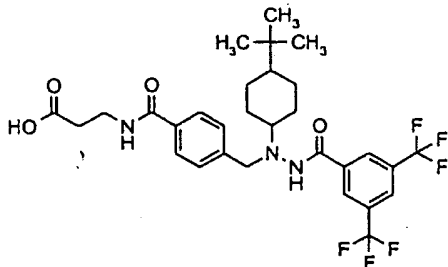
$^1\text{H}$  NMR (DMSO):  $\delta$  9.23 (s, 1H); 8.42 (t, 1H); 7.72 (dd, 4H); 7.50 (d, 2H); 7.42 (d, 2H); 4.15 (s, 2H).

HPLC-MS (Method B):  $m/z$  = 562.4 ( $M+1$ ).  $R_t$  = 7.24 min.

20

**EXAMPLE 428 (general procedure (R))**

3-{4-[N'-(3,5-Bis(trifluoromethyl)benzoyl)-N-(4-*tert*-butylcyclohexyl)hydrazinomethyl]benzoylamino}propionic acid



5

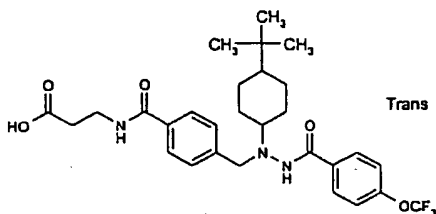
$^1\text{H}$  NMR (DMSO):  $\delta$  9.55 (s, 1H); 8.46 (t, 1H); 8.26 (s, 2H); 7.75 (d, 2H); 7.50 (d, 2H); 4.18 (s, 2H); 0.85 (s, 9H).

HPLC-MS (Method B):  $m/z$  = 616.4 (M+1).  $R_t$  = 8.11 min.

10

**EXAMPLE 429**

3-{4-[N-(*trans*-4-*tert*-Butylcyclohexyl)-N'-(4-trifluoromethoxybenzoyl)hydrazinomethyl]-benzoylamino}propionic acid



15

To an ice-cooled solution of hydrazine hydrate (16 mL, 25% (w/w), 125 mmol) in THF (100 mL) was added a solution of 4-trifluoromethoxybenzoyl chloride (4.3 g, 19.2 mmol) in THF (50 mL) over 30 min. The solution was stirred for a further 30 min and then diluted with ether (200 mL). The turbid organic solution was then washed with water (3 x 200 mL) and brine (200 mL). After drying ( $\text{Na}_2\text{SO}_4$ ), solvent was removed by rotary evaporation. The solid residue was dissolved in ethanol/water (1:1, 200 mL), insoluble material was filtered off, and the filtrate taken to dryness to leave 3.63 g (86%) of pure 4-trifluoromethoxybenzoic acid hydrazide.

20

$^1\text{H}$  NMR (DMSO- $d_6$ ), 300 MHz:  $\delta$  9.90 (s, 1H); 7.92 (d, 2H); 7.45 (d, 2H), 4.52 (bs, 2H).

25

HPLC-MS (Method B):  $R_t$  = 4.04 min,  $m/z$  = 221 (M+1).

The above 4-trifluoromethoxybenzoic acid hydrazide (3.60 g, 16.3 mmol) and 4-*tert*-butylcyclohexanone (2.52 g, 16.3 mmol) was dissolved in ethanol (150 mL) and the solution was heated to reflux. After 30 min, powdered sodium borohydride (0.96 g, 25.2 mmol) was carefully added, and the mixture stirred for an additional 30 min at reflux. The reaction was cooled to 25°C, and remains of sodium borohydride were quenched by addition of acetic acid (10 mL). The volume of the reaction mixture was reduced to one third by rotary evaporation before adding water (100 mL) and diethyl ether (200 mL). The organic phase was then collected, washed once with brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The organic phase was taken to dryness, and the residual oil purified by column chromatography (silica gel G 60, ethyl acetate/heptane (1:4)) to afford the pure *trans* and *cis* isomers of 4-trifluoromethoxybenzoic acid *N'*-(4-*tert*-butylcyclohexyl)hydrazide.

*trans* isomer: TLC: R<sub>f</sub> = 0.10 ethyl acetate/heptane (1:4).

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>), 300 MHz: δ 10.04 (s, 1H); 7.94 (d, 2H); 7.45 (d, 2H); 4.98 (bs, 1H); 2.65 (m, 1H); 1.06-1.95 (m, 4H); 0.86-1.12 (m, 5H); 0.80 (s, 9H).

*cis* isomer: TLC: R<sub>f</sub> = 0.25 ethyl acetate/heptane (1:4).

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>), 300 MHz: δ 10.02 (s, 1H); 7.96 (d, 2H); 7.45 (d, 2H); 4.89 (bs, 1H); 3.08 (s, 1H); 1.85 (m, 2H); 1.31-1.52 (m, 6H); 0.95 (m, 1H); 0.85 (s, 9H).

*trans*-3-[4-[*N*-(4-*tert*-Butylcyclohexyl)-*N'*-(4-trifluoromethoxybenzoyl)hydrazinomethyl]benzoyl-amino}propionic acid

*trans*-4-Trifluoromethoxybenzoic acid *N'*-(4-*tert*-butylcyclohexyl)hydrazide (715 mg, 2 mmol) was dissolved in DMSO (8 mL), and added to 3-[4-(bromomethyl)benzoyl]aminopropanoic acid derivatized Wang resin (2.0 g, loading app. 0.5 mmol/g) prepared as described in example 1. The mixture was heated to 80°C for 24 hours, and then cooled. After draining, the resin was washed with DMSO (3 x), DMF (3 x) and dichloromethane (10 x). A 50% TFA/dichloromethane solution (8 mL) was then added, and the mixture was left for 30 min at 25°C. The supernatant was collected, and the resin subsequently washed once with a 50% TFA/dichloromethane solution (8 mL). The combined supernatant and washing were taken to dryness by rotary evaporation, to leave a brown oil. Further purification by column chromatography (silica G60, 400 mesh, 48% ethyl acetate, 48% heptane, 4% acetic acid), and crystallization (ethanol/water) gave the title compound as fine needles.

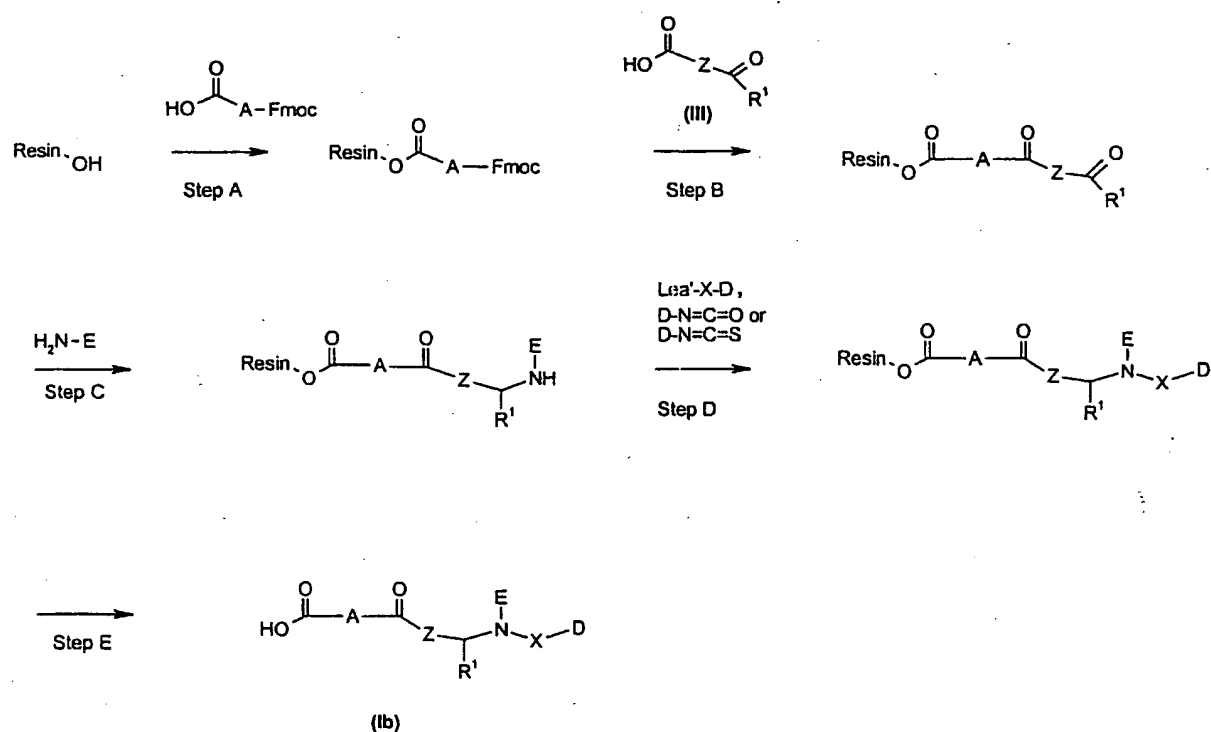
$R_f = 0.15$  ethyl acetate/heptane (1:1).

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ), 300 MHz:  $\delta$  12.18 (s, 1H); 9.20 (s, 1H); 8.42 (t, 1H); 7.74 (d, 2H); 7.72 (d, 2H); 4.47 (d, 2H); 7.38 (d, 2H); 4.12 (s, 2H); 3.42 (dt, 2H); 2.82 (m, 1H); 2.50 (t, 2H); 2.04 (bd, 2H); 1.77 (bd, 2H); 1.24 (m, 2H); 0.96 (m, 3H); 0.82 (s, 9H).

HPLC-MS (Method B):  $R_t = 7.57$  min,  $m/z = 564$  (M+1).

10 General procedure (S) for the solid phase synthesis of compounds of the general formula (Ib):

Steps B and C are modified compared to general procedure (C) so that step C is a reductive amination of a resin bound aldehyde or ketone:



15

wherein

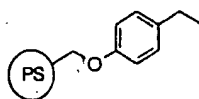
A, Z,  $R^1$ , E and D are as defined for formula (I),

20 X is  $-\text{S(O)}_2-(\text{CH}_2)_r-$ ,  $-\text{C(O)NH-}$  or  $-\text{C(S)NH-}$ , wherein r is as defined for formula (I),

Lea' is a leaving group such as -OSu, chloro, phenoxy or 4-nitrophenoxy, and

Resin denotes a polystyrene resin with a linker such as the Wang linker:

5



wherein PS denotes polystyrene.

10 Step B:

The Fmoc protecting group is removed using a solution of 20% piperidine in DMF which is added to the resin and vortexed for 0.5 hours. After draining the resin is washed with DMF containing 1-hydroxybenzotriazole (50 mg/mL) and DMF.

- 15 The acylation (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 78) is performed by adding an excess of acid (III) in a solvent such as DMF, *N*-methylpyrrolidinone, THF, dichloromethane, 1,2-dichloroethane, acetonitrile, DMSO or a mixture of two or more of these, optionally in the presence of a base such as *N*-methylmorpholine, triethylamine, diisopropylethylamine, dicyclohexylmethylamine or another tertiary amine, followed by a coupling
- 20 reagent such as dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1,1'-carbonyldiimidazole, 2-(1*H*-9-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate or bromo-tris-pyrrolidinophosphonium hexafluorophosphate in a solvent such as DMF, *N*-methylpyrrolidinone, THF, dichloromethane, 1,2-dichloroethane, acetonitrile, DMSO or a mixture of two or more of these, optionally in the presence of a side reaction inhibitor such as 3-
- 25 hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine, *N*-hydroxybenzotriazole or 1-hydroxy-7-azabenzotriazole. The reaction is performed between 20°C and 40°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed several times with the solvent used during the reaction.

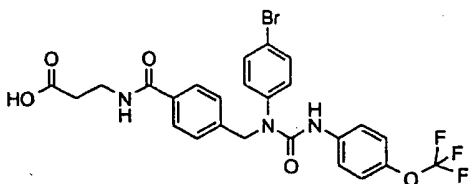
30 Step C:

The reaction is generally known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 133) and is generally performed by stirring resin bound aldehyde or ketone with an excess of amine at low pH (by addition of an acid, such as acetic acid or formic acid) in a solvent such as THF, DMF, *N*-methylpyrrolidinone, methanol, ethanol, DMSO, dichloro-

methane, 1,2-dichloroethane, trimethyl orthoformate, triethyl orthoformate, or a mixture of two or more of these. As reducing agent sodium cyanoborohydride may be used. The reaction is performed between 20°C and 120°C, preferably at 25°C.

5 EXAMPLE 430 (general procedure (S))

3-{4-[1-(4-Bromophenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



10 <sup>1</sup>H NMR (DMSO): δ 6.52 (2H, d), 7.20 (2H, d), 7.43 (2H, d), 7.77 (2H, d), 8.47 (1H, t).

Step A: Resin bound Fmoc β-alanine

15 150 μmol Fmoc β-alanine was dissolved in 500 μL of a mixture of DMF and diisopropylethylamine (430:70) and added to 50 mg polystyrene resin functionalised with a Wang linker. 200 μmol PyBrOP dissolved in DMF (500 μL) was added. After shaking the suspension for 4 hours at 25°C, the resin was isolated by filtration and washed with 3 x 1 mL DMF.

Step B: Resin bound 3-(4-formylbenzoylamino)propionic acid

20 To the above resin bound Fmoc β-alanine was added 1000 μL of a 20% solution of piperidine in DMF. Upon shaking for 30 min, the resin was drained and washed with 1 mL DMF containing 1-hydroxybenzotriazole (50 mg/mL) and DMF (2 x 1 mL). Then 200 μmol 4-formylbenzoic acid (30 mg) and diisopropylethylamine (70 μL) were dissolved in DMF (430 μL) and added to the resin followed by 200 μmol PyBrOP dissolved in DMF (500 μL). The mixture was shaken for 4 hours at 25°C followed by filtration and washing of the resin with DMF (3 x 1 mL) and trimethylorthoformate (1 x 1 mL).

Step C: Resin bound 3-{4-[(4-bromophenylamino)methyl]benzoylamino}propionic acid

30 The above resin bound 3-(4-formylbenzoylamino)propionic acid (50 mg) was treated with a solution of 4-bromoaniline (500 μmol) in a mixture of DMF (500 μL) and trimethylorthoformate (500 μL). Glacial acetic acid (100 μL) was added and the mixture was shaken for 1 hour at 25°C. Sodium cyanoborohydride (750 μmol) suspended in a mixture of DMF and trimethyl-

orthoformate (1:1, 1 mL) was added and the mixture was vortexed at 25°C for 16 hours followed by filtration and washing with a mixture of DMF and water (4:1, 2 x 1 mL) followed by 3 x 1 mL DMF and 2 x 1 mL dichloromethane to afford the desired product.

5 Step D: Resin bound 3-{4-[1-(4-bromophenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino}propionic acid

200 µmol 4-trifluoromethoxyphenylisocyanate dissolved in 500 µL dichloromethane was added to the above resin bound 3-{4-[(4-bromophenylamino)methyl]benzoylamino}propionic acid (50 mg). Shaking the mixture for 16 hours at 25°C followed by filtration and washing of  
10 the resin with 4 x 1 mL DMF, 2 x 1 mL water, 3 x 1 mL THF and 5 x 1 mL dichloromethane afforded the resin bound title compound.

Step E: 3-{4-[1-(4-Bromophenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

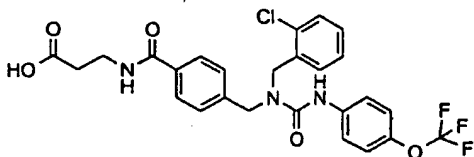
15 The above resin bound 3-{4-[1-(4-bromophenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino}propionic acid (50 mg) was treated with 1 mL 50% TFA in dichloromethane for 1 hour at 25°C. The product was filtered off and the resin was washed with 1 mL dichloromethane. The combined extracts were concentrated in vacuo. The residue was purified by preparative HPLC to afford the title compound.

20

The following compounds were made according to the general procedure (S):

EXAMPLE 431 (general procedure (S))

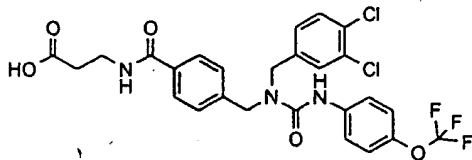
25 3-{4-[1-(2-Chlorobenzyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



<sup>1</sup>H NMR (DMSO): δ 4.63 (2H, s), 4.65 (2H, s), 7.2-7.4 (7H, m), 7.47 (1H, d), 7.61 (2H, d), 7.81 (2H, d), 8.49 (1H, t), 8.90 (1H, s).

**EXAMPLE 432 (general procedure (S))**

3-{4-[1-(3,4-Dichlorobenzyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

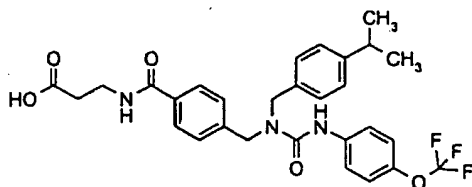


5

<sup>1</sup>H NMR (DMSO): δ 8.85 (s, 1H); 8.46 (t, 1H); 7.80 (d, 2H); 7.61 (d, 2H); 7.59 (s, 1H); 7.50 (s, 1H); 7.35 (d, 2H); 7.25 (d, 2H); 7.23 (s, 1H); 4.65 (s, 2H); 4.52 (s, 2H); 3.46 (q, 2H); 2.50 (t, 2H).

**10 EXAMPLE 433 (general procedure (S))**

3-{4-[1-(4-Isopropylbenzyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

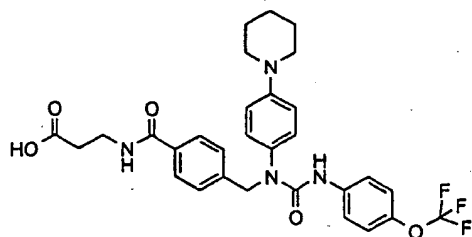


15 <sup>1</sup>H NMR (DMSO): δ 8.80 (s, 1H); 8.51 (t, 1H); 7.82 (d, 2H); 7.60 (d, 2H); 7.30 d, 2H); 7.25 (d, 2H); 7.21 (d, 2H); 7.18 (d, 2H); 4.61 (s, 2H); 4.55 (s, 1H); 3.46 (q, 2H); 1.20 (d, 6H).

**EXAMPLE 434 (general procedure (S))**

3-{4-[1-(4-Piperidin-1-ylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

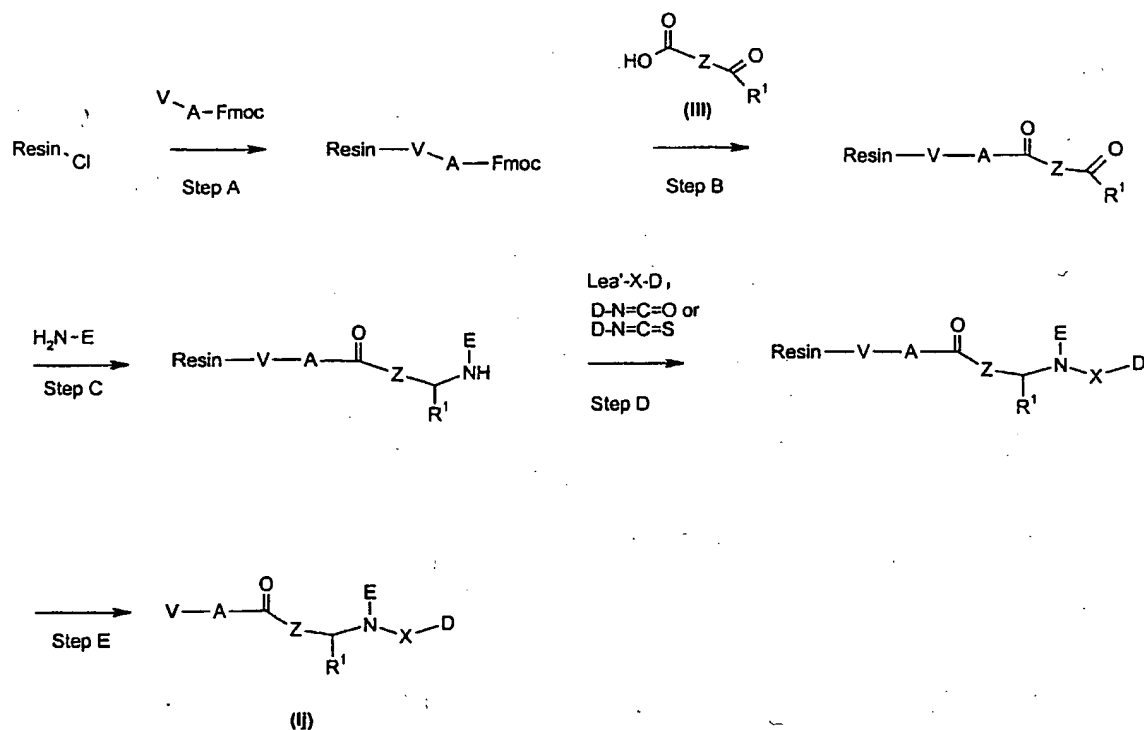
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<sup>1</sup>H NMR (DMSO): δ 8.46 (t, 1H); 8.10 (s, 1H); 7.78 (d, 2H); 7.55 (d, 2H); 7.35 (d, 2H); 7.25 (d, 2H); 7.12 (d, 2H); 7.05 (d, 2H); 4.90 (s, 2H).



General procedure (T) for the solid phase synthesis of compounds of the general formula (II):  
Alternatively, the solid support used in general procedure (S) can be a 2-chlorotrityl polystyrene resin.



wherein

V, A, Z, R<sup>1</sup>, E and D are as defined for formula (I),

X is -C(O)NH- or -C(S)NH- and

Lea<sup>1</sup> is a leaving group such as -OSu, chloro, phenoxy or 4-nitrophenoxy.

#### Step A:

The reaction is known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 24) and is generally performed by shaking a suspension of the resin with a solution of a nucleophilic Fmoc protected amine (V-A-Fmoc) in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine. Typical solvents are pyridine, dichloromethane, 1,2-dichloroethane, DMF, N-methylpyrrolidinone, THF, DMSO or mixtures of two or more of these. The reaction is performed between 20°C

and 120°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed with any solvent mentioned above including mixtures hereof, containing a base as mentioned above and an alcohol, typically methanol, as a scavenger of unreacted resin bound 2-chlorotriylchloride.

5

Step B:

Step B is identical to step B of general procedure (S).

Step C:10 

Step C is identical to step C of general procedure (S).

Step D:

Step D is identical to step D of general procedure (S).

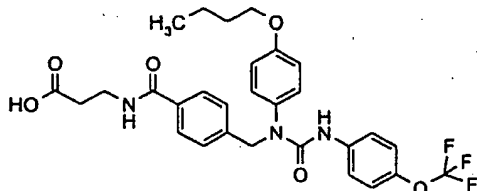
15

Step E:

Step E is identical to step E of general procedure (S).

EXAMPLE 435 (general procedure (T))

3-{4-[1-(4-Butoxyphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic  
20 acid

Step A: Resin bound Fmoc  $\beta$ -alanine25 

150  $\mu$ mol Fmoc  $\beta$ -alanine was dissolved in a mixture of 250  $\mu$ L dichloromethane, 250  $\mu$ L DMF and 100  $\mu$ L diisopropylethylamine and added to 50 mg polystyrene resin functionalized with a 2-chlorotriyl linker. After shaking the suspension for 4 hours at 25°C, the resin was isolated by filtration and washed with 2 x 1 mL dichloromethane: methanol:diisopropylethylamine 17:2:1 and 2 x 1 mL DMF.

Step B: Resin bound 3-(4-formylbenzoylamino)propionic acid

To the above resin bound Fmoc  $\beta$ -alanine was added 500  $\mu$ L of a 20% solution of piperidine in DMF. After 30 min of shaking, the resin was drained and washed with 1 mL DMF containing 1-hydroxybenzotriazole (50 mg/mL) and DMF (2 x 1 mL). Then 200  $\mu$ mol 4-formylbenzoic acid (30 mg) and 200  $\mu$ mol HOBt (31 mg) dissolved in DMF (500  $\mu$ L) were added to the resin followed by 200  $\mu$ mol diisopropyl carbodiimide (DIC, 25.2 mg) dissolved in acetonitrile (500  $\mu$ L). The mixture was shaken for 4 hours at 25°C followed by filtration and washing of the resin with DMF (3 x 1 mL).

Step C: Resin bound 3-(4-[(4-Butoxyphenylamino)methyl]benzoylamino)propionic acid

The above resin bound 3-(4-formylbenzoylamino)propionic acid (50 mg) was treated with a 0.5 M solution of 4-butoxyaniline (0.25 mmol, 41.25 mg) in a mixture of DMF and trimethyl-orthoformate (1:1, 0.5 mL) and glacial acetic acid (50  $\mu$ L) for 1 hour at 25 °C. Sodium cyanoborohydride (250  $\mu$ mol, 16 mg) dissolved in a mixture of DMF and methanol (1:1, 0.25 mL) was added, and the mixture was vortexed at 25°C for 4 hours followed by filtration and washing with a mixture of DMF and methanol (1:1, 2 x 1 mL) 3 x 1 mL DMF and 2 x 1 mL dichloromethane to afford the desired product.

Step D: Resin bound 3-(4-[1-(4-Butoxyphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino)propionic acid

200  $\mu$ mol 4-trifluoromethoxyphenylisocyanate dissolved in 500  $\mu$ L dichloroethane was added to the above resin bound 3-(4-[(4-butoxyphenylamino)methyl]benzoylamino)propionic acid (50 mg). Shaking the mixture 5 hours at 25°C followed by filtration and washing of the resin with 2 x 1 mL dichloromethane, 4 x 1 mL DMF, 2 x 1 mL H<sub>2</sub>O, 3 x 1 mL THF and 3 x 1 mL dichloromethane afforded the resin bound title compound.

Step E: 3-(4-[1-(4-Butoxyphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino)propionic acid

The above resin bound 3-(4-[1-(4-butoxyphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino)propionic acid (50 mg) was treated with 1 mL 5% TFA in dichloromethane for 1 hour at 25°C. The product was filtered off and the resin was washed with 1 mL dichloromethane. The combined extracts were concentrated in vacuo. The residue was dissolved in 50  $\mu$ L DMSO + 500  $\mu$ L acetonitrile and purified by preparative HPLC using a Supelcosil ABZ+ 25 cm x 10 mm 5 $\mu$  column. The starting eluent composition was 5% acetonitrile in water changing over 30 min to 90% acetonitrile in water which was then kept constant for 5 min

before going back to the starting composition over 10 min. The flow rate was kept constant at 8 mL/min collecting one fraction pr. minute. The process was monitored using an UV detector operating at 214 nm. The fractions containing the desired product were combined and evaporated in vacuo to afford the title compound.

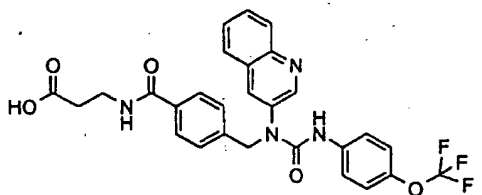
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<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 12.20 (s br, 1H); 8.50 (t, 1H); 8.09 (s, 1H); 7.73 (d, 2H); 7.55 (d, 2H); 7.30 (d, 2H); 7.20 (d, 2H); 7.10 (d, 2H); 6.90 (d, 2H); 4.90 (s, 2H); 3.95 (t, 2H); 3.45 (m, 2H); 2.50 (t, 2H); 1.60 (k, 2H) 1.42 (sx, 2H); 0.95 (t, 3H)

10 The following examples can be made as described above.

EXAMPLE 436 (general procedure (T))

3-{4-[1-Quinolin-3-yl-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

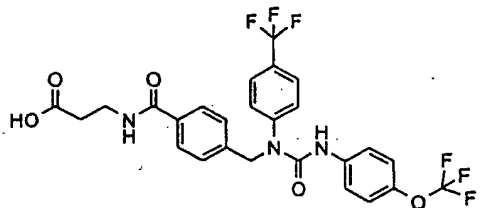


15

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 12.20 (s br, 1H); 8.80 (m, 2H); 8.45 (t, 1H); 8.25 (s, 1H); 8.00 (d, 2H); 7.95 (d, 2H); 7.78 (m, 3H); 7.60 (t, 1H); 7.55 (d, 2H); 7.38 (d, 2H); 7.24 (d, 2H); 5.12 (s, 2H); 3.45 (m, 2H); 2.50 (t, 2H).

20 EXAMPLE 437 (general procedure (T))

3-{4-[3-(4-Trifluoromethoxyphenyl)-1-(4-trifluoromethylphenyl)ureidomethyl]benzoylamino}-propionic acid

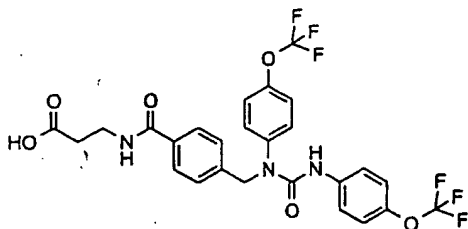


25

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 12.15 (s br, 1H); 8.95 (s, 1H); 8.48 (t, 1H); 7.75 (d, 2H); 7.68 (d, 2H); 7.58 (d, 2H); 7.50 (d, 2H); 7.35 (d, 2H); 7.25 (d, 2H); 5.10 (s, 2H); 3.45 (m, 2H); 2.50 (t, 2H).

**EXAMPLE 438 (general procedure (T))**

3-[4-[1,3-Bis(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino]propionic acid

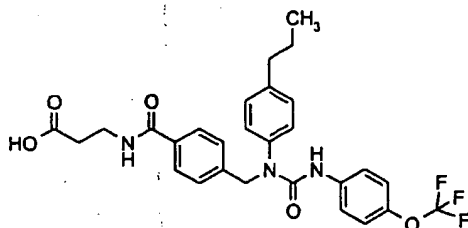


5

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 12.25 (s br, 1H); 8.65 (s, 1H); 8.48 (t, 1H); 7.75 (d, 2H); 7.55 (d, 2H); 7.35 (m, 6H); 7.22 (d, 2H); 5.00 (s, 2H); 3.40 (m, 2H); 2.50 (t, 2H).

**EXAMPLE 439 (general procedure (T))**

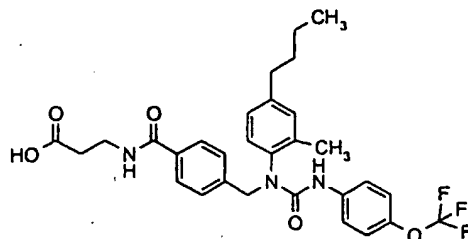
10 3-{4-[1-(4-Propylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic  
acid



<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 12.20 (s, 1H); 8.45 (t, 1H); 8.30 (s, 1H); 7.73 (d, 2H); 7.52 (d, 2H); 7.32 (d, 2H); 7.20-7.10 (m, 6H); 4.95 (s, 2H); 3.45 (m, 2H); 2.50 (m, 4H); 1.60 (sx, 2H); 0.90 (t, 3H).

**EXAMPLE 440 (general procedure (T))**

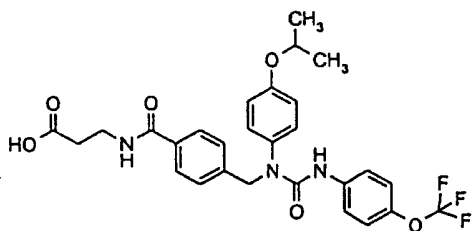
20 3-(4-[1-(4-Butyl-2-methylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino)-  
propionic acid



<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 12.20 (s br, 1H); 8.45 (t, 1H); 7.87 (s, 1H); 7.75 (d, 2H); 7.52 (d, 2H); 7.30 (d, 2H); 7.22 (d, 2H); 7.10 (s, 1H) 7.05 (d, 1H); 6.95 (d, 1H); 5.15-4.85 (d br, 2H); 3.45 (m, 2H); 2.55-2.50 (m, 4H); 1.60 (k, 2H); 1.32 (sx, 2H); 0.90 (t, 3H).

5 EXAMPLE 441 (general procedure (T))

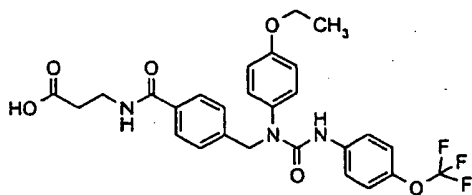
3-{4-[1-(4-Isopropoxyphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



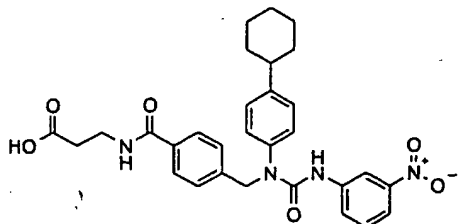
10 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.47 (t, 1H); 8.10 (s, 1H); 7.75 (d, 2H); 7.56 (d, 2H); 7.36 (d, 2H); 7.23 (d, 2H); 7.12 (d, 2H); 6.90 (d, 2H); 4.92 (s, 2H); 4.60 (q, 1H); 1.25 (d, 6H).

EXAMPLE 442 (general procedure (T))

3-{4-[1-(4-Ethoxyphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.46 (t, 1H); 8.06 (s, 1H); 7.78 (d, 2H); 7.56 (d, 2H); 7.34 (d, 2H); 7.22 (d, 2H); 7.14 (d, 2H); 6.92 (d, 2H); 4.91 (s, 2H); 4.01 (q, 2H); 1.32 (t, 3H).

EXAMPLE 443 (general procedure (T))3-{4-[1-(4-Cyclohexylphenyl)-3-(3-nitrophenyl)ureidomethyl]benzoylamino}propionic acid

- 5  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ ):  $\delta$  12.20 (s br, 1H); 8.78 (s, 1H); 8.45 (s+t, 2H); 7.92(d, 1H); 7.80 (d, 1H); 7.75 (d, 2H); 7.50 (t, 1H) 7.30 (d, 2H); 7.20 (d, 2H); 7.15 (d,2H); 4.95 (s, 2H); 3.45 (m, 2H); 2.50 (t, 2H); 1.90-1.10 (m, 11H)

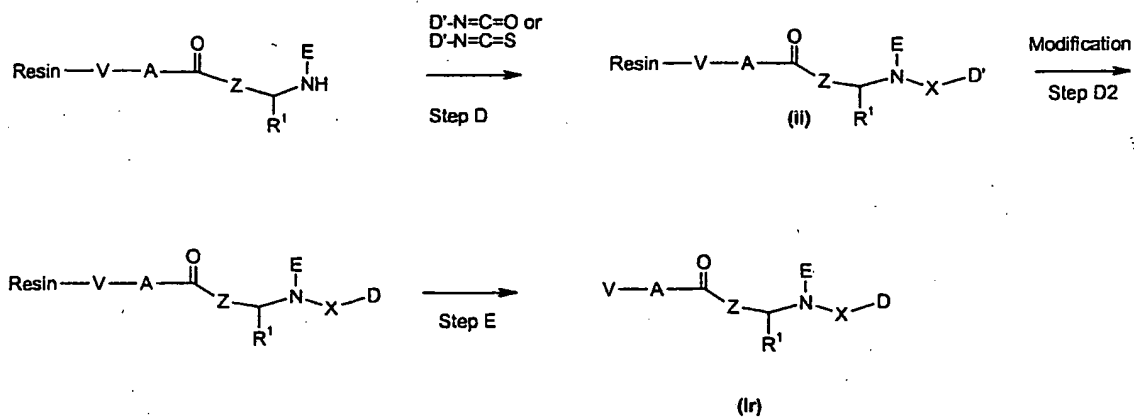
HPLC-MS (Method B):  $m/z = 545$  ( $M+1$ ).  $R_t = 7.47$  min

10

General procedure (U) for the solid phase synthesis of compounds of the general formula (Ir):

Alternatively, molecules of general formula (Ii) obtained by the previously described general method (T) may be modified after step D. This applies to all general procedures comprising a

15 step similar to step D of procedure (T):



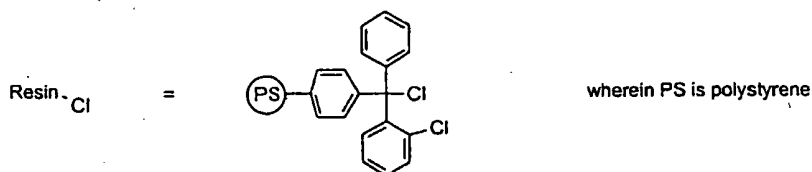
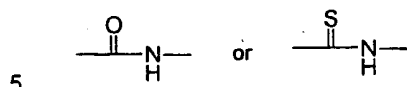
wherein

20

A, V, Z,  $R^1$ , E and D are as defined for formula (I),

D' is a subgroup of D containing functionalities that may be further derivatized like sulfides, sulfoxides, or esters,

X is



#### Step D2: Oxidation of sulfides or sulfoxides

- 10 The reaction is known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 132) and is performed by treating the resin bound intermediate with an oxidizing agent like 3-chloroperoxybenzoic acid or peracetic acid in a solvent like dichloromethane, 1,2-dichloroethane, THF or a mixture thereof. The reaction is performed between 20°C and 120°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed with dichloro-
- 15 methane, 1,2-dichloroethane, DMF, *N*-methylpyrrolidinone, THF, DMSO or mixtures of two or more of these.

#### Step D2: Derivatization of esters

- Ester hydrolysis. The reaction is known (Hoekstra et al, Bioorg. Med. Chem. Lett. 1996, 6, 2371-2376) and is performed by treating the resin bound intermediate with a solution of potassium trimethylsilanolate in a solvent like THF or dioxan. The reaction is performed between 20°C and 120°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed with dichloromethane, 1,2-dichloroethane, dioxan, DMF, *N*-methylpyrrolidinone, THF, DMSO or mixtures of two or more of these in combination with an acid like acetic acid
- 25 to afford the corresponding resin bound carboxylic acid.

- The above resin bound carboxylic acid is converted into an active ester by the use of pentafluorophenyl trifluoroacetate or 4-nitrophenyl trifluoroacetate in the presence of pyridine in a solvent such as DMF, *N*-methylpyrrolidinone, THF, dichloromethane, 1,2-dichloroethane, acetonitrile, DMSO or a mixture of two or more of these. The reaction is performed between
- 30

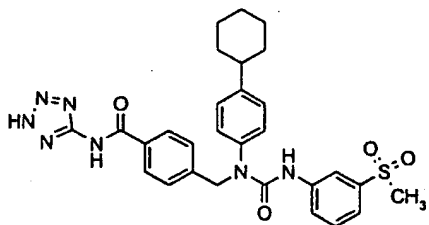


20°C and 40°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed several times with the solvent used during the reaction.

The above resin bound active ester is allowed to react with nucleophiles like ammonia, primary or secondary amines, *N*-hydroxyamidines or hydrazides to afford resin bound carboxylic acid derivatives.

EXAMPLE 444 (general procedure (U))

4-[1-(4-Cyclohexylphenyl)-3-(3-methylsulfonylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



Step A: Resin bound 4-formyl-*N*-(2*H*-tetrazol-5-yl)benzamide

150 µmol 4-formyl-*N*-(2*H*-tetrazol-5-yl)benzamide was dissolved in a mixture of 250 µL dichloromethane, 250 µL DMF and 100 µL diisopropylethylamine and added to 50 mg polystyrene resin functionalized with 2-chlorotriyl chloride. After shaking the suspension for 4 hours at 25°C, the resin was isolated by filtration and washed with 2 x 1 mL dichloromethane:-methanol:diisopropylethylamine 17:2:1 and 2 x 1 mL DMF.

Step C: Resin bound 4-[(4-cyclohexylphenylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

The above resin bound 4-formyl-*N*-(2*H*-tetrazol-5-yl)benzamide (50 mg) was treated with a 0.5 M solution of 4-cyclohexylaniline (0.25 mmol, 41.25 mg) in a mixture of DMF and trimethylorthoformate (1:1, 0.5 mL) and glacial acetic acid (50 µL) for 1 hour at 25°C followed sodium cyanoborohydride (250 µmol, 16 mg) dissolved in a mixture of DMF and methanol (1:1, 0.25 mL). Shaking at 25°C for 4 hours followed by filtration and washing with a mixture of DMF and methanol (1:1, 2 x 1 mL), 3 x 1 mL DMF and 2 x 1 mL dichloromethane afforded the desired product.

Step D: Resin bound 4-[1-(4-cyclohexylphenyl)-3-(3-methylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

200 µmol 3-Thiomethylphenylisocyanate dissolved in 500 µL dichloroethane was added to the above resin bound 4-[(4-cyclohexylphenylamino)methyl]-N-(2H-tetrazol-5-yl)benzamide (50 mg). Shaking the mixture 5 hours at 25°C followed by filtration and washing with 2 x 1 mL dichloromethane, 4 x 1 mL DMF, 2 x 1 mL H<sub>2</sub>O, 3 x 1 mL THF and 3 x 1 mL dichloromethane afforded the resin bound title compound.

Step D2: Resin bound 4-[1-(4-Cyclohexylphenyl)-3-(3-methylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

To the above resin bound 4-[1-(4-cyclohexylphenyl)-3-(3-methylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide was added a solution of 3-chloroperbenzoic acid (2.0-2.8 mmol) in 1,2-dichloroethane (500 µL). The mixture was shaken overnight at 25 °C. Filtration followed by washing of the resin with dichloromethane (2 x 1 mL) afforded the resin bound title compound.

Step E: 4-[1-(4-Cyclohexylphenyl)-3-(3-methylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

The above resin bound 4-[1-(4-cyclohexylphenyl)-3-(3-methylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide (50 mg) was washed with DMF (4 x 1 mL), H<sub>2</sub>O (2 x 1 mL), THF (3 x 1 mL) and dichloromethane (3 x 1 mL) and treated with 1 mL 5% TFA in dichloromethane for 1 hour at 25°C. The product was filtered off and the resin was washed with 1 mL dichloromethane. The combined extracts were concentrated in vacuo. The residue was dissolved in 50 µL DMSO + 500 µL acetonitrile and purified by preparative HPLC using a Supelcosil ABZ+ 25 cm x 10 mm 5µ column. The starting eluent composition was 5% acetonitrile in water changing over 30 min to 90% acetonitrile in water which was then kept constant for 5 min before going back to the starting composition over 10 min. The flow rate was kept constant at 8 mL/min collecting one fraction pr. minute. The process was monitored using an UV detector operating at 214 nm. The fractions containing the desired product were combined and evaporated in vacuo to afford the title compound.

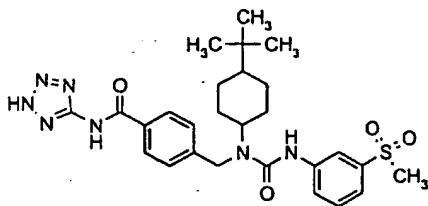
<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 12.30 (s br, 1H); 8.70 (s, 1H); 8.05 (d, 2H); 7.75 (m, 1H); 7.52-7.42 (m, 4H); 7.20 (s, 4H); 5.00 (s, 2H); 3.15 (s, 3H); 1.85-1.60 (m, 5H); 1.50-1.15 (m, 6H).

HPLC-MS (method B)  $m/z$  = 574,  $R_t$  = 7.18 min.

The following examples can be made as described above.

5 EXAMPLE 445 (general procedure (U))

4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-methylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



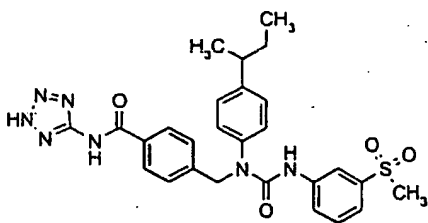
- 10  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  12.30 (s br, 1H); 8.82 (s, 1H); 8.05 (d, 2H); 8.15-8.00 (m, 3H); 7.78 (d, 1H); 7.55-7.45 (m, 4H); 4.65 (s, 2H); 4.10 (t br, 1H); 3.13 (s, 3H); 1.83-0.90 (m, 9H); 0.85 (s, 9H).

HPLC-MS (method B)  $m/z$  = 554,  $R_t$  = 7.12 min.

15

EXAMPLE 446 (general procedure (U))

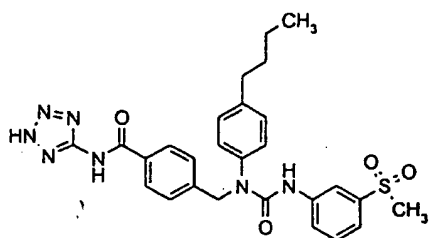
4-[1-(4-*sec*-Butylphenyl)-3-(3-methylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



20

- $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  12.35 (s br, 1H); 8.65 (s, 1H); 8.10-8.00 (m, 4H); 7.75 (m, 1H); 7.52-7.42 (m, 4H); 7.20 (s, 4H); 5.00 (s, 2H); 3.15 (s, 3H); 2.55 (q, 1H); 1.55 (k, 2H); 1.20 (d, 3H); 0.75 (t, 3H).

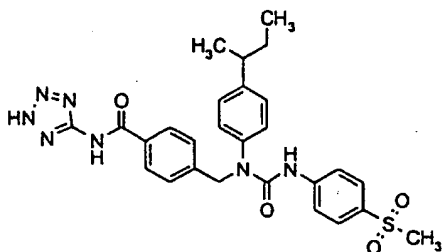
- 25 HPLC-MS (method B)  $m/z$  = 548,  $R_t$  = 6.03 min.

EXAMPLE 447 (general procedure (U))4-[1-(4-Butylphenyl)-3-(3-methylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

- 5  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  0.90 (3H, t), 1.42 (2H, sextet), 1.57 (2H, pentet), 2.58 (2H, partly hidden by DMSO), 3.15 (3H, s), 5.02 (2H, s), 7.21 (4H, s), 7.45-7.52 (4H, m), 7.85 (1H, m), 8.0-8.1 (3H, m), 8.61 (1H, s), 12.4 (1H, bs).

HPLC-MS (Method B):  $R_t$  = 6.37 min,  $m/z$  = 548 ( $M + 1$ ).

10

EXAMPLE 448 (general procedure (U))4-[1-(4-sec-Butylphenyl)-3-(4-methylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide

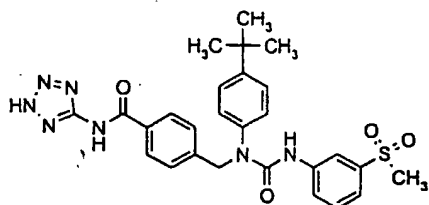
15

- $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  12.30 (s br, 1H); 8.72 (s, 1H); 8.05 (d, 2H); 7.75 (d, 2H); 7.70 (d, 2H); 7.45 (d, 2H); 7.20 (s, 4H); 5.00 (s, 2H); 3.11 (s, 3H); 2.60 (q, 1H); 1.55 (k, 2H); 1.20 (d, 3H); 0.75 (t, 3H).

- 20 HPLC-MS (method B)  $m/z$  = 548,  $R_t$  = 6.03 min.

EXAMPLE 449 (general procedure (U))

4-[1-(4-*tert*-Butylphenyl)-3-(3-methylsulfonylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



5

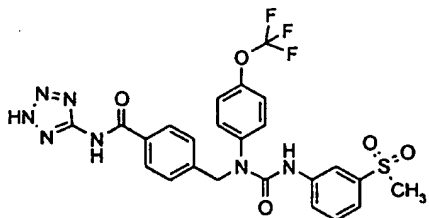
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.30 (9H, s), 3.18 (3H, s), 5.03 (2H, s), 7.24 (2H, d), 7.41 (2H, d), 7.45-7.55 (8H, m), 7.85 (1H, m), 8.05 (2H, d), 8.08 (1H, s), 8.70 (1H, s), 12.4 (1H, bs).

HPLC-MS (Method B):  $R_t$  = 5.97 min,  $m/z$  = 548 ( $M + 1$ ).

10

EXAMPLE 450 (general procedure (U))

4-[3-(3-Methylsulfonylphenyl)-1-(4-trifluoromethoxyphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



15

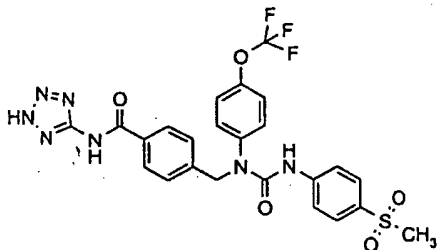
$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  12.35 (s, 1H); 8.85 (s, 1H); 8.05 (d, 2H); 7.75 (m, 1H); 7.55-7.35 (m, 9H); 7.20 (s, 4H); 5.05 (s, 2H); 3.15 (s, 3H).

HPLC-MS (method B)  $m/z$  = 576,  $R_t$  = 5.42 min.

20

EXAMPLE 451 (general procedure (U))

4-[3-(4-Methylsulfonylphenyl)-1-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

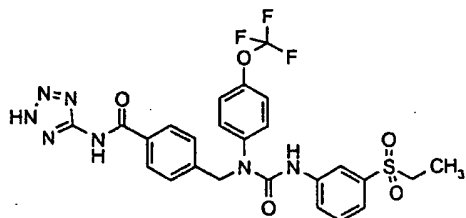
$^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  12.35 (s, 1H); 8.95 (s, 1H); 8.05 (d, 2H); 7.70 (d, 2H); 7.65 (d, 2H); 7.49 (d, 2H); 7.43 (d, 2H); 7.45 (d, 2H); 5.05 (s, 2H); 3.12 (s, 3H).

HPLC-MS (method B)  $m/z$  = 576,  $R_t$  = 5.42 min.

10

EXAMPLE 452 (general procedure (U))

4-[3-(3-Ethylsulfonylphenyl)-1-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

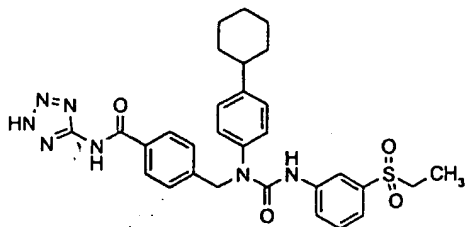


15

HPLC-MS (method B)  $m/z$  = 590,  $R_t$  = 5.90 min.

EXAMPLE 453 (general procedure (U))

4-[1-(4-Cyclohexylphenyl)-3-(3-ethylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



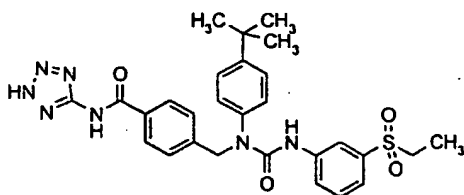
5

HPLC-MS (method B)  $m/z$  = 588,  $R_t$  = 7.10 min.

EXAMPLE 454 (general procedure (U))

4-[1-(4-*tert*-Butylphenyl)-3-(3-ethylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide

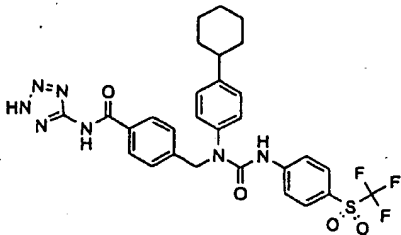
10



HPLC-MS (method B)  $m/z$  = 561,  $R_t$  = 6.40 min.

EXAMPLE 455 (general procedure (U))

4-[1-(4-Cyclohexylphenyl)-3-(4-trifluoromethylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

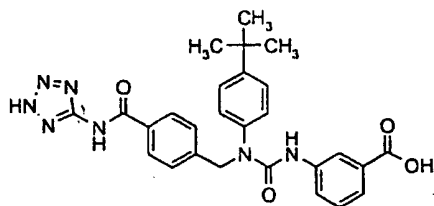


20  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  9.20 (1H, broad), 7.90 (5H, m), 7.79 (1H, dd), 7.44 (2H, d), 7.21 (4H, s), 5.00 (2H, broad), 1.90-1.00 (10H, m).

HPLC-MS (method B): m/z: 628,  $R_t$  = 8.05 min.

EXAMPLE 456 (general procedure (U))

3-[3-(4-*tert*-Butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido]benzoic acid



5

Step A: Resin bound 4-formyl-*N*-(2*H*-tetrazol-5-yl)benzamide

1500  $\mu$ mol 4-formyl-*N*-(2*H*-tetrazol-5-yl)benzamide was dissolved in a mixture of 2500  $\mu$ L dichloromethane, 2500  $\mu$ L DMF and 1000  $\mu$ L diisopropylethylamine and added to 500 mg  
10 polystyrene resin functionalized with 2-chlorotriyl chloride. After shaking the suspension for 4 hours at 25°C, the resin was isolated by filtration and washed with 2 x 10 mL dichloromethane: methanol:diisopropylethylamine 17:2:1 and 2 x 10 mL DMF.

Step C: Resin bound 4-[(4-*tert*-butylphenylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

15 The above resin bound 4-formyl-*N*-(2*H*-tetrazol-5-yl)benzamide (500 mg) was treated with a 0.5 M solution of 4-*tert*-butylaniline (2.5 mmol, 412.5 mg) in a mixture of DMF and trimethyl-orthoformate (1:1, 5 mL) and glacial acetic acid (500  $\mu$ L) for 1 hour at 25°C followed by sodium cyanoborohydride (2.5 mmol, 160 mg) dissolved in a mixture of DMF and methanol (1:1, 2.5 mL). Shaking at 25°C for 4 hours followed by filtration and washing with a mixture of  
20 methanol and DMF (1:1, 2 x 10 mL), DMF (3 x 10 mL) and dichloromethane (2 x 10 mL) afforded the desired product.

Step D: Resin bound 3-[3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido]benzoic acid methyl ester

25 2.50 mmol 3-isocyanatobenzoic acid methyl ester dissolved in 5 mL dichloroethane was added to the above resin 4-[(4-*tert*-butylphenylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide (500 mg). Shaking the mixture 5 hours at 25°C followed by filtration and washing of the resin with dichloromethane (2 x 10 mL), DMF (2 x 10 mL) and THF (3 x 10 mL) afforded the resin bound title compound.

30



Step D2: Derivatization of estersResin bound 3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzoic acid

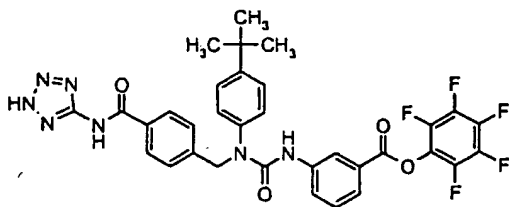
To the above resin bound 3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzoic acid methyl ester was added a solution of potassium trimethylsilanolate in THF (1M, 5 mL). The mixture was shaken 4 hours at 25°C, filtered and allowed to react with a solution of acetic acid in THF (20%, 5 mL) at 25°C overnight. Filtration followed by washing of the resin with dichloromethane (2 x 10 mL) afforded the resin bound title compound.

Step E: 3-{3-(4-*tert*-Butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzoic acid

The above resin bound 3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzoic acid (500 mg) was washed with DMF (4 x 10 mL), H<sub>2</sub>O (2 x 10 mL), THF (3 x 10 mL), dichloromethane (3 x 10 mL) and treated with 10 mL 5% TFA in dichloromethane for 1 hour at 25°C. The product was filtered off and the resin was washed with 10 mL dichloromethane. The combined extracts were concentrated in vacuo. The residue was recrystallised in acetonitrile to afford the title compound.

<sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 12.90 (s br, 1H); 12.35 (s br, 1H); 8.50 (s, 1H); 8.05 (d, 2H); 7.75 (d, 1H) 7.60-7.15 (m, 8H); 5.00 (s, 2H); 1.22 (s, 9H).

HPLC-MS (method B) *m/z* = 514, *R*<sub>t</sub> = 5.98 min.

EXAMPLE 457 (general procedure (U))3-{3-(4-*tert*-Butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzoic acid pentafluorophenyl ester

Step D2: Derivatisation of esters

Resin bound 3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzoic acid pentafluorophenyl ester

To the above resin bound 3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzoic acid was added a solution of pyridine (500  $\mu$ L) in DMF (5 mL) followed by pentafluorophenyl trifluoroacetate (850  $\mu$ L). The mixture was shaken for 4 hours at 25 °C, filtered and washed with DMF (2 x 10 mL), affording the resin bound title compound.

Step E: 3-{3-(4-*tert*-Butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzoic acid pentafluorophenyl ester

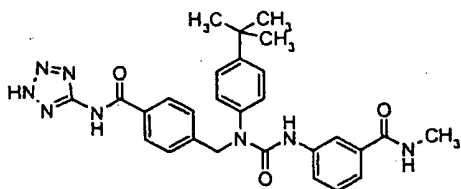
The above resin bound 3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzoic acid pentafluorophenyl ester (500 mg) was washed with DMF (4 x 10 mL), H<sub>2</sub>O (2 x 10 mL), THF (3 x 10 mL), dichloromethane (3 x 10 mL) and treated with 10 mL 5% TFA in dichloromethane for 1 hour at 25°C. The product was filtered off and the resin was washed with 10 mL dichloromethane. The combined extracts were concentrated in vacuo. The residue was recrystallised in CH<sub>3</sub>CN to afford the title compound.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  12.30 (s br, 1H); 8.05 (d, 2H); 8.00-7.60 (m, 2H) 7.55-7.15 (m, 8H); 5.00 (s, 2H); 1.22 (s, 9H).

HPLC-MS (method B)  $m/z$  = 680,  $R_t$  = 8.27 min.

EXAMPLE 458 (general procedure (U))

*N*-Methyl-3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzamide

Step D2: Derivatisation of esters

Resin bound *N*-methyl-3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzamide

To the above resin bound 3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzoic acid pentafluorophenyl ester was added a solution of methylamine in THF

(2M, 5 mL). The mixture was shaken at 25 °C overnight, filtered and washed with THF (2 x 10 mL), affording the resin bound title compound.

Step E: N-Methyl-3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}-benzamide

The above resin bound *N*-methyl-3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)-benzyl]ureido}benzamide (500 mg) was washed with DMF (4 x 10 mL), H<sub>2</sub>O (2 x 10 mL), THF (3 x 10 mL), dichloromethane (3 x 10 mL) and treated with 10 mL 5% TFA in dichloromethane for 1 hour at 25°C. The product was filtered off and the resin was washed with 10 mL dichloromethane. The combined extracts were concentrated in vacuo. The residue was recrystallized from CH<sub>3</sub>CN to afford the title compound.

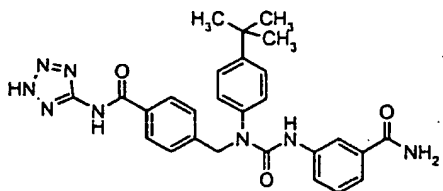
<sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 12.35 (s br, 1H); 8.40 (s, 1H); 8.43 (q, 1H); 8.05 (d, 2H); 7.85 (s, 1H); 7.63 (d, 1H); 7.50-7.15 (m, 8H); 5.03 (s, 2H); 2.80 (d, 3H); 1.25 (s, 9H).

HPLC-MS (method B): *m/z* = 527, *R*<sub>t</sub> = 5.55 min

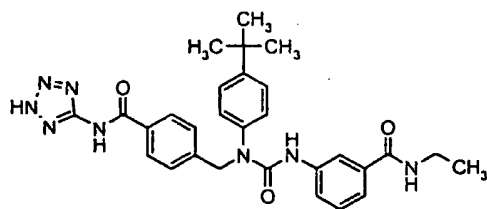
The following examples were made as described above.

EXAMPLE 459 (general procedure (U))

3-{3-(4-*tert*-Butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzamide



HPLC-MS (method B): *m/z* = 513, *R*<sub>t</sub> = 5.52 min.

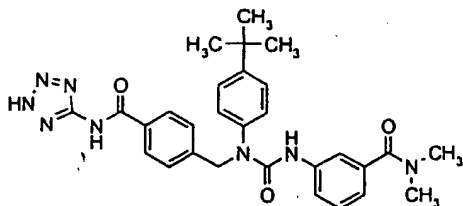
EXAMPLE 460 (general procedure (U))N-Ethyl-3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}benzamide

- 5  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  12.35 (s br, 1H); 8.40 (m, 2H); 8.05 (d, 2H); 7.80 (s, 1H); 7.63 (d, 1H); 7.55-7.15 (m, 8H); 5.03 (s, 2H); 3.30 (dq, 2H); 1.30 (s, 9H); 1.12 (t, 3H).

HPLC-MS (method B):  $m/z$  = 541,  $R_t$  = 5.83 min.

EXAMPLE 461 (general procedure (U))

*N,N*-Dimethyl-3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}-benzamide



5

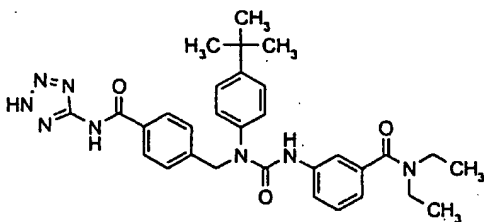
$^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  12.35 (s br, 1H); 8.40 (s, 1H); 8.05 (d, 2H); 7.55-7.15 (m, 9H); 6.98 (d, 1H); 5.03 (s, 2H); 2.95 (d, br, 6H); 1.30 (s, 9H).

HPLC-MS (method B):  $m/z$  = 541,  $R_t$  = 5.80 min.

10

Example 462 (general procedure (U))

*N,N*-Diethyl-3-{3-(4-*tert*-butylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]ureido}-benzamide



15

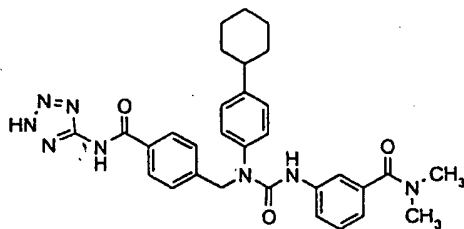
$^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  12.35 (s br, 1H); 8.40 (s, 1H); 8.05 (d, 2H); 7.50-7.18 (m, 9H); 6.95 (d, 1H); 5.01 (s, 2H); 3.24 (s, br, 4H); 1.30 (s, 9H); 1.10 (s, br, 6H).

HPLC-MS (method B)  $m/z$  = 569,  $R_t$  = 6.77 min.

20

**EXAMPLE 463 (general procedure (U))**

*N,N*-Dimethyl-3-{3-(4-cyclohexylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)-benzyl]ureido}benzamide



5

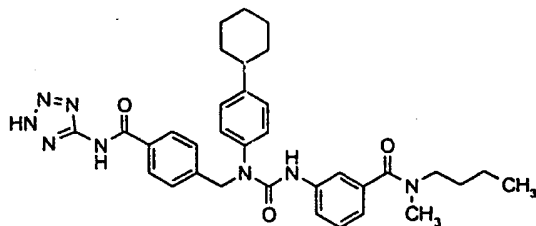
$^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  12.30 (s br, 1H); 8.35 (s, 1H); 8.05 (d, 2H); 7.50 (m, 4H); 7.20 (m, 5H); 6.95 (d, 1H); 5.00 (s, 2H); 3.15 (s, 3H); 2.94 (d br, 6H); 1.85-1.15 (m, 11H).

HPLC-MS (method B):  $m/z$  = 567,  $R_t$  = 6.47 min.

10

**EXAMPLE 464 (general procedure (U))**

*N*-Butyl-*N*-methyl-3-{3-(4-cyclohexylphenyl)-3-[4-(2*H*-tetrazol-5-ylcarbamoyl)-benzyl]ureido}-benzamide

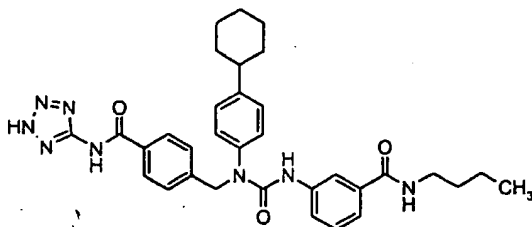


15

$^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  12.30 (s br, 1H); 8.35 (s, 1H); 8.05 (d, 2H); 7.48 (m, 4H); 7.35-7.20 (m, 5H); 6.95 (d, 1H); 5.00 (s, 2H); 2.92 (d br, 3H); 1.85-0.70 (m, 18H).

HPLC-MS (method B):  $m/z$  = 609,  $R_t$  = 7.51 min.

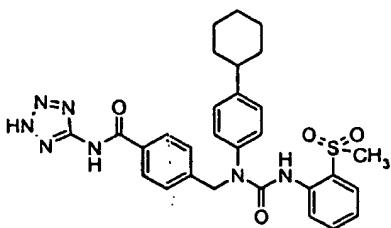
20

EXAMPLE 465 (general procedure (U))N-Butyl-3-(3-(4-cyclohexylphenyl)-3-[4-(2H-tetrazol-5-ylcarbamoyl)-benzyl]ureido)benzamide

- 5 <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 11.35 (s br, 1H); 8.55 (m, 2H); 8.05 (d, 2H); 7.70 (s, 1H); 7.62 (d, 1H); 7.42 (m, 3H); 7.35-7.10 (m, 5H); 5.00 (s, 2H); 1.85-1.10 (m, 15H); 0.90 (t, 3H).

HPLC-MS (method B): *m/z* = 595, *R*<sub>t</sub> = 7.48 min.

10 EXAMPLE 466 (general procedure (U))

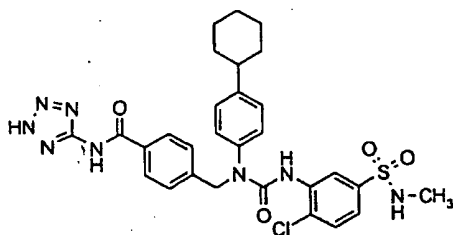
4-[1-(4-Cyclohexylphenyl)-3-(2-methylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide

- 15 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 12.40 (s, 1H); 8.50-8.45 (s+d, 2H); 8.05 (d, 2H); 7.68 (d, 1H); 7.65 (t, 1H); 7.52 (d, 2H); 7.22 (s, 4H); 7.18 (t, 1H); 5.00 (s, 2H); 3.00 (s, 3H); 1.85-1.65 (m, 5H); 1.50-1.15 (m, 5H)

HPLC-MS (Method B): *m/z* = 574 (M+1). *R*<sub>t</sub> = 7.38 min

EXAMPLE 467 (general procedure (U))

4-[3-(2-Chloro-5-methylsulfonylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

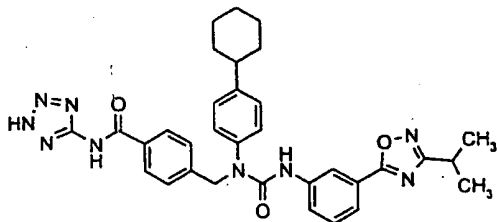
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  8.5 (d, 1H); 7.76 (d br, 2H); 7.60-7.35 (m, 5H); 7.32 (s, 4H); 5.00 (s, 2H); 2.43 (d, 3H); 1.85-1.65 (m, 5H); 1.50-1.15 (m, 5H)

HPLC-MS (Method B):  $m/z$  = 623 (M+1).  $R_t$  = 7.82 min.

10

EXAMPLE 468 (general procedure (U))

4-[1-(4-Cyclohexylphenyl)-3-[3-(3-isopropyl-1,2,4-oxadiazol-5-yl)phenyl]ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



15

The oxadiazole was prepared by using *N*-hydroxy-isobutyramidine as nucleophile instead of an amine as described in example 458. After cleavage from the resin, ring closure to the oxadiazole was conducted in refluxing toluene.

20  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  12.05 (s br, 1H); 8.68 (s, 1H); 8.28 (s, 1H); 8.05 (d, 2H); 7.80 (d, 1H); 7.63 (d, 1H); 7.55-7.45 (m, 3H); 7.20 (s, 4H); 5.04 (s, 2H); 3.12 (h, 1H); 1.85-1.65 (m, 5H); 1.50-1.15 (m+d, 11H)

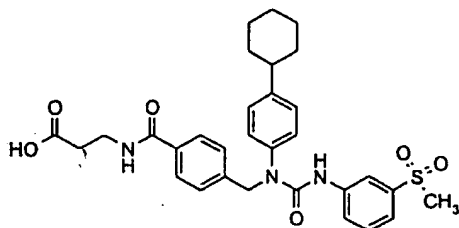
HPLC-MS (Method B):  $m/z$  = 624 (M+1).  $R_t$  = 8.07 min.

25



EXAMPLE 469 (general procedure (U))

3-[4-[1-(4-Cyclohexylphenyl)-3-(3-methylsulfonylphenyl)ureidomethyl]benzoylamino]-propionic acid



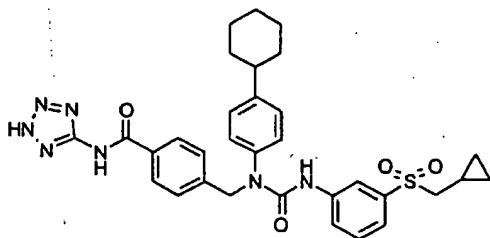
5

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  8.65 (s, 1H); 8.51 (t, 1H); 8.05 (s, 1H); 8.78 (m, 1H); 7.75 (d, 2H); 7.45 (m, 2H); 7.30 (d, 2H); 7.22 (d, 2H); 7.12 (d, 2H); 4.95 (s, 2H); 3.40 (m); 3.15 (s, 3H); 2.43 (t, 2H); 1.90-1.15 (m)

10 HPLC-MS (Method B):  $m/z$  = 578 ( $M+1$ ).  $R_t$  = 6.32 min.

EXAMPLE 470 (general procedure (U))

4-[1-(4-Cyclohexylphenyl)-3-(3-cyclopropylmethylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

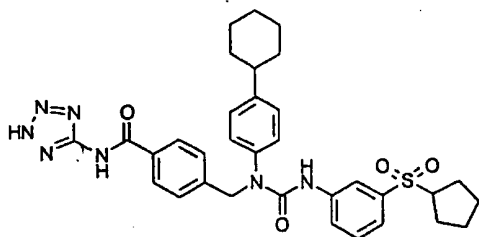


15

HPLC-MS (method B):  $m/z$ : 614,  $R_t$  = 7.35 min.

EXAMPLE 471 (general procedure (U))

4-[1-(4-Cyclohexylphenyl)-3-(3-cyclopentylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



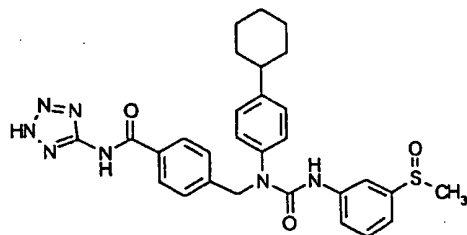
5

HPLC-MS (method B):  $m/z$ : 628,  $R_t$  = 7.55 min.

EXAMPLE 472 (general procedure (U))

4-[1-(4-Cyclohexylphenyl)-3-(3-methylsulfinylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide

10



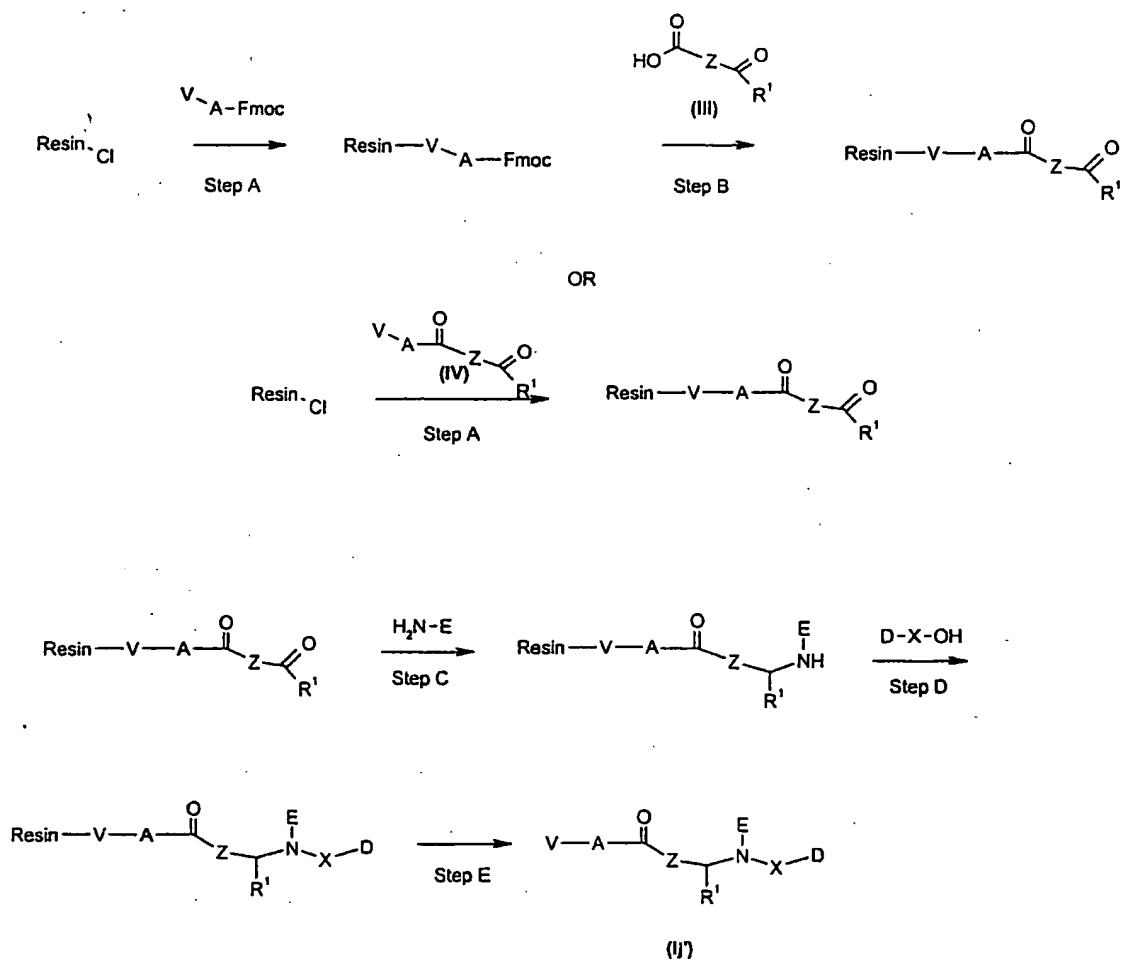
$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  8.58(s, 1H), 7.99(d, 2H), 7.80(s, 1H), 7.63(d, 1H), 7.42(d, 2H), 7.40(d, 1H), 7.20(dd, 4H), 5.00(s, 2H), 2.70(s, 3H), 1.85-1.15 (m, 10H).

15

HPLC-MS (method B):  $m/z$ : 558,  $R_t$  = 6.22 min.

General procedure (V) for the solid phase synthesis of compounds of the general formula (II'):

Alternatively, the solid support used in general procedure (B) can be a 2-chlorotrityl polystyrene resin.



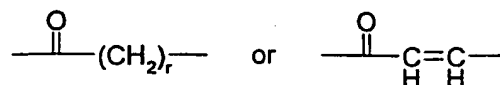
5

wherein

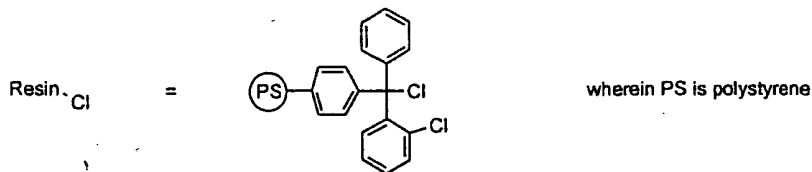
V, A, Z, R<sup>1</sup>, E and D are as defined for formula (I),

10

X is



wherein r is as defined for formula (I), and



#### 5 Step A:

The reaction is known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 24) and is generally performed by shaking a suspension of the resin with a solution of a nucleophilic Fmoc protected amine (V-A-Fmoc) or (IV) in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine.

- 10 Typical solvents are pyridine, dichloromethane, 1,2-dichloroethane, DMF, NMP, THF, DMSO or mixtures of two or more of these. The reaction is performed between 20°C and 120°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed with any solvent mentioned above including mixtures hereof, containing a base as mentioned above and an alcohol, typically methanol, as a scavenger of unreacted resin bound 2-chlorotritylchloride.

15

#### Step B:

Step B is identical to step B of general procedure (S).

#### Step C:

- 20 Step C is identical to step C of general procedure (S).

#### Step D:

The acylation (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 78) is performed by adding an excess of D-X-OH in a solvent such as DMF, *N*-methylpyrrolidinone,

- 25 THF, dichloromethane, 1,2-dichloroethane, 1,2-dichloropropane, acetonitrile, DMSO or a mixture of two or more of these, optionally in the presence of a base such as *N*-methylmorpholine, triethylamine, diisopropylethylamine, dicyclohexylmethylamine or another tertiary amine, followed by a coupling reagent such as dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1,1'-carbonyldiimidazole, 2-(1*H*-9-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (PyBrOP) or bromo-tris-pyrrolidinophosphonium hexafluorophosphate in a solvent such as DMF, *N*-methylpyrrolidinone, THF, dichloromethane, 1,2-
- 30

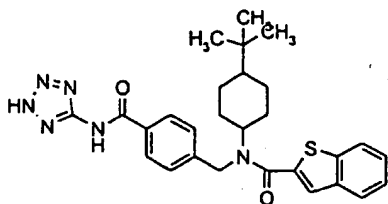
dichloroethane, 1,2-dichloropropane, acetonitrile, DMSO or a mixture of two or more of these, optionally in the presence of a side reaction inhibitor such as 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine, *N*-hydroxybenzotriazole or 1-hydroxy-7-azabenzotriazole. The reaction is performed between 20°C and 60°C, preferably at 50°C. Excess reagents are filtered off and the resin is washed several times with the solvent used during the reaction.

#### Step E:

Step E is identical to step E of general procedure (S).

#### 10 EXAMPLE 473 (general procedure (V))

Benzo[*b*]thiophene-2-carboxylic acid (4-*tert*-butylcyclohexyl)-[4-(2*H*-tetrazol-5-ylcarbamoyl)-benzyl]amide



#### 15 Step A: Resin bound 4-formyl-*N*-(2*H*-tetrazol-5-yl)benzamide

150 µmol 4-formyl-*N*-(2*H*-tetrazol-5-yl)benzamide was dissolved in a mixture of 250 µL dichloromethane, 250 µL DMF and 100 µL diisopropylethylamine and added to 50 mg polystyrene resin functionalized with 2-chlorotriyl chloride. After shaking the suspension for 4 hours at 25°C, the resin was isolated by filtration and washed with 2 x 1 mL dichloromethane: methanol:diisopropylethylamine 17:2:1 and 2 x 1 mL DMF.

#### Step C: Resin bound 4-[(4-*tert*-butylcyclohexylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

The above resin bound 4-formyl-*N*-(2*H*-tetrazol-5-yl)benzamide (50 mg) was treated with a 0.5 M solution of 4-*tert*-butylcyclohexylamine (0.25 mmol, 38.75 mg) in a mixture of NMP and trimethylorthoformate (1:1, 0.5 mL) and glacial acetic acid (50 µL) for 1 hour at 25°C followed by sodium cyanoborohydride (250 µmol, 16 mg) dissolved in a mixture of NMP and methanol (1:1, 0.25 mL). Shaking at 25°C for 4 hours followed by filtration and washing with a mixture of NMP and methanol (1:1, 2 x 1 mL); NMP (3 x 1 mL) and a mixture of 1,2-dichloropropane (DCP) and diisopropylethylamine (7:1, 2 x 1 mL) afforded the desired product.

Step D: Resin bound benzo[b]thiophene-2-carboxylic acid (4-*tert*-butylcyclohexyl)-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]amide

To the above resin bound 4-[(4-*tert*-butylcyclohexylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide was added a solution of benzo[b]thiophene-2-carboxylic acid (400  $\mu$ mol) in a mixture of NMP, DCP and diisopropylethylamine (4.5:4.5:1, 1 mL) followed by a solution of Py-BrOP (400  $\mu$ mol) in DCP (500  $\mu$ L). The mixture was allowed to react 3 hours at 50 °C. The resin was cooled to 25 °C while washed with NMP (4 x 1 mL), and DCM (10 x 1 mL).

Step E: Benzo[b]thiophene-2-carboxylic acid (4-*tert*-butylcyclohexyl)-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]amide

The above resin bound benzo[b]thiophene-2-carboxylic acid (4-*tert*-butylcyclohexyl)-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]amide (50 mg) was treated with 1.2 mL 20% trifluoroacetic acid in dichloromethane for 1 hour at 25°C. The product was filtered off and concentrated in vacuo to afford the title compound.

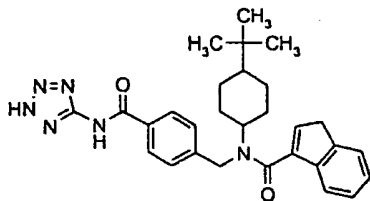
<sup>1</sup>H NMR (DMSO):  $\delta$  8.14 (d, 2H); 8.1-7.9 (m, 2H); 7.81 (s, 2H); 7.60-7.50 (m, 3H); 4.96 (s, 1H); 4.89 (s br, 1H).

HPLC-MS (Method D):  $m/z$  = 517 (M+1).  $R_t$  = 5.80 min.

The following examples can be made as described above.

EXAMPLE 474 (general procedure (V))

3*H*-Indene-1-carboxylic acid (4-*tert*-butylcyclohexyl)-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]-amide

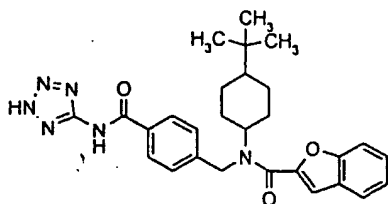


<sup>1</sup>H NMR (DMSO):  $\delta$  8.15 (d, 2H); 7.70-7.30 (m, 6H); 6.82 (d, 1H)

HPLC-MS (Method E):  $m/z$  = 499 (M+1).  $R_t$  = 3.07 min.

EXAMPLE 475 (general procedure (V))

Benzofuran-2-carboxylic acid (4-*tert*-butylcyclohexyl)-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]-  
amide



5

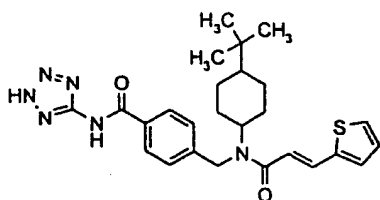
$^1\text{H}$  NMR (DMSO. Isomers ca 1:1):  $\delta$  8.13 (d, 2H); 7.95-7.65 (m, 2H); 7.56 (d, 2H); 7.55-7.30 (m, 2H); 4.88 (s br, 2H); 4.23 (s br, 1H).

HPLC-MS (Method E):  $m/z$  = 501 ( $M+1$ ).  $R_t$  = 3.20 min.

10

EXAMPLE 476 (general procedure (V))

4-[[[(4-*tert*-Butylcyclohexyl)-(3-thiophen-2-ylacryloyl)amino]methyl]-*N*-(2*H*-tetrazol-5-yl)-  
benzamide



15

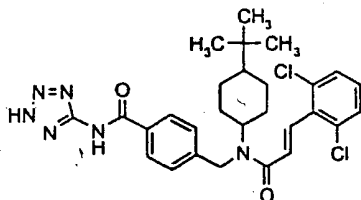
$^1\text{H}$  NMR (DMSO. Isomers ca 1:1):  $\delta$  8.20-8.05 (m, 2H); 7.80-7.40 (m, 4H); 7.40-6.85 (2H); 4.87 (s, 1H); 4.75 (s, 1H).

HPLC-MS (Method E):  $m/z$  = 495 ( $M+1$ ).  $R_t$  = 3.07 min.

20

**EXAMPLE 477 (general procedure (V))**

4-(((4-*tert*-Butylcyclohexyl)-[3-(2,6-dichlorophenyl)acryloyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)benzamide



5

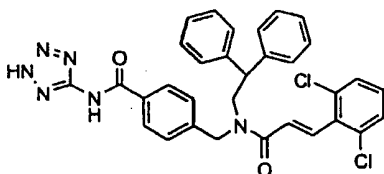
<sup>1</sup>H NMR (DMSO. Isomers ca 1:1):  $\delta$  8.20 (m, 2H); 7.60 (m, 6H); 6.84 (d, 1H); 4.88(s, 1H); 4.78 (s, 1H).

HPLC-MS (Method E):  $m/z$  = 555 (M+1).  $R_t$  = 3.39, 3.45 min.

10

**EXAMPLE 478 (general procedure (V))**

4-(((3-(2,6-Dichlorophenyl)acryloyl)-(2,2-diphenylethyl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide



15

<sup>1</sup>H NMR (DMSO. Isomers ca 1:1):  $\delta$  8.11 (s, 2H); 7.70-7.25 (m, 16 H); 7.20 (d, 1H); 6.93 (d, 1H); 4.63 (s, 1H); 4.57 (s, 1H); 4.50 (t, 1H); 4.26 (d, 2H).

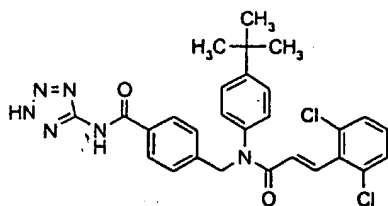
HPLC-MS (Method E):  $m/z$  = 598 (M+1).  $R_t$  = 3.09 min.

20



EXAMPLE 479 (general procedure (V))

4-((4-*tert*-butylphenyl)-[3-(2,6-dichlorophenyl)acryloyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide



5

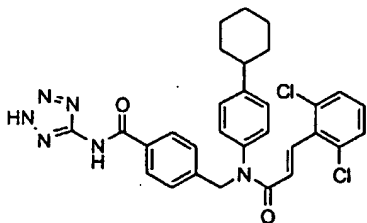
$^1\text{H}$  NMR (DMSO):  $\delta$  8.10 (d, 2H); 7.68 (d, 1H); 7.56-7.48 (m, 6H); 7.41 (t, 1H); 7.26 (d, 2H); 6.56 (d, 1H); 5.17 (s, 2H).

HPLC-MS (Method E):  $m/z$  = 549 (M+1).  $R_t$  = 3.47 min.

10

EXAMPLE 480 (general procedure (V))

4-((4-Cyclohexylphenyl)-[3-(2,6-dichlorophenyl)acryloyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide

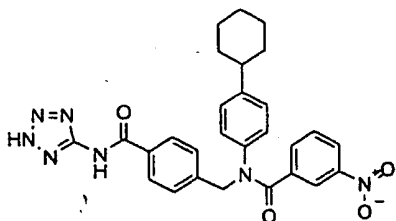


15

$^1\text{H}$  NMR (DMSO):  $\delta$  8.07 (d, 2H); 7.67 (d, 1H); 7.55 (d, 2H); 7.49 (d, 2H); 7.40 (t, 1H); 7.32 (d, 2H); 7.23 (d, 2H); 6.55 (d, 1H); 5.16 (d, 2H).

HPLC-MS (Method E):  $m/z$  = 575 (M+1).  $R_t$  = 3.76 min.

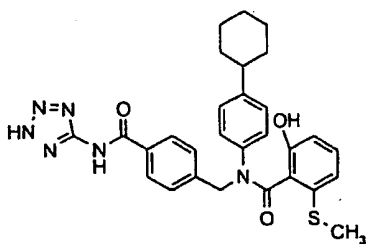
20

**EXAMPLE 481 (general procedure (V))**4-[[[(4-Cyclohexylphenyl)-(3-nitrobenzoyl)amino]methyl]-N-(2H-tetrazol-5-yl)benzamide

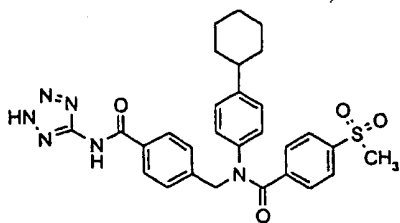
- 5 <sup>1</sup>H NMR (DMSO): δ 8.20 (d, 1H); 8.17 (s, 1H); 8.09 (d, 2H); 7.81 (d, 1H); 7.60 (m, 3H); 7.14 (dd, 4H); 5.29 (s, 2H).

HPLC-MS (Method E): m/z = 526 (M+1). R<sub>t</sub> = 3.18 min.

10 **EXAMPLE 482 (general procedure (V))**

4-[[[(4-Cyclohexylphenyl)-(2-hydroxy-6-methylsulfanylbenzoyl)amino]methyl]-N-(2H-tetrazol-5-yl)benzamide

- 15 HPLC-MS (Method E): m/z = 543 (M+1). R<sub>t</sub> = 3.25 min.

**EXAMPLE 483 (general procedure (V))**4-[[[(4-Cyclohexylphenyl)-(4-methylsulfonylbenzoyl)amino]methyl]-N-(2H-tetrazol-5-yl)-benzamide

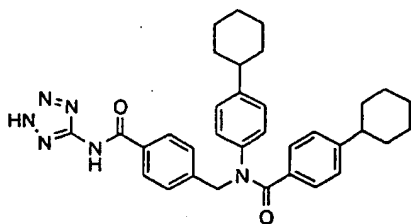
<sup>1</sup>H NMR (DMSO): δ 8.09 (d, 2H); 8.09 (d, 4H); 7.84 (d, 2H); 7.65 (d, 2H); 7.57 (m, 3-4H); 7.12 (s, 4H); 5.24 (s, 2H).

HPLC-MS (Method E): m/z = 559 (M+1); R<sub>t</sub> = 2.77 min.

5

EXAMPLE 484 (general procedure (V))

4-(((4-Cyclohexylphenyl)-(4-cyclohexylbenzoyl)amino)methyl)-N-(2H-tetrazol-5-yl)benzamide

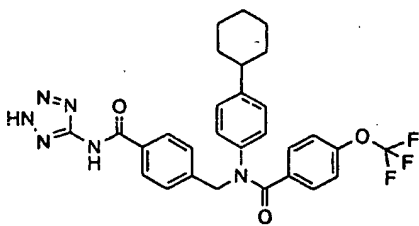


10 <sup>1</sup>H NMR (DMSO): δ 8.08 (d, 2H) 7.53 (d, 2H); 7.30 (d, 2H); 7.15-7.05 (m, 6H); 5.21 (s, 2H).

HPLC-MS (Method E): m/z = 563 (M+1). R<sub>t</sub> = 3.99 min.

EXAMPLE 485 (general procedure (V))

15 4-(((4-Cyclohexylphenyl)-(4-trifluoromethoxybenzoyl)amino)methyl)-N-(2H-tetrazol-5-yl)-benzamide

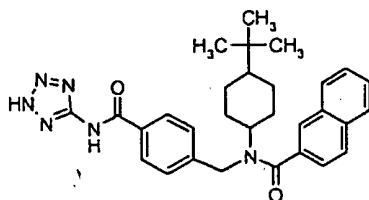


20 <sup>1</sup>H NMR (DMSO): δ 8.09 (d, 2H); 7.56 (d, 2H); 7.51 (d, 2H); 7.28 (d, 2H); 7.10 (dd, 4H); 5.24 (s, 2H).

HPLC-MS (Method E): m/z = 565(M+1). R<sub>t</sub> = 3.52 min.

EXAMPLE 486 (general procedure (V))

Naphtalene-2-carboxylic acid (4-*tert*-butylcyclohexyl)-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]-  
amide



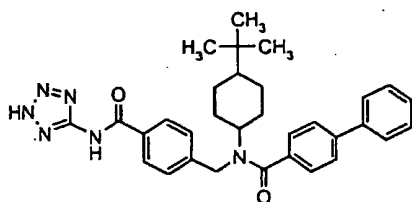
5

HPLC-MS (Method E):  $m/z$  = 511 ( $M+1$ ).  $R_t$  = 3.47 min.

EXAMPLE 487 (general procedure (V))

Biphenyl-4-carboxylic acid (4-*tert*-butylcyclohexyl)-[4-(2*H*-tetrazol-5-ylcarbamoyl)benzyl]-  
amide

10

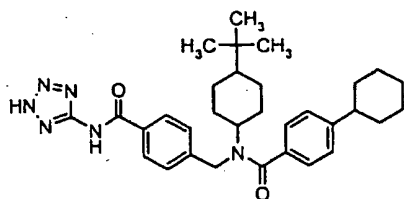


$^1\text{H}$  NMR (DMSO):  $\delta$  8.15 (d, 2H); 7.90-7.40 (m, 9H); 4.84 (s, 2H).

15 HPLC-MS (Method D):  $m/z$  = 537 ( $M+1$ ).  $R_t$  = 6.13 min.

EXAMPLE 488 (general procedure (V))

4-(((4-*tert*-Butylcyclohexyl)-(4-cyclohexylbenzoyl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-  
benzamide

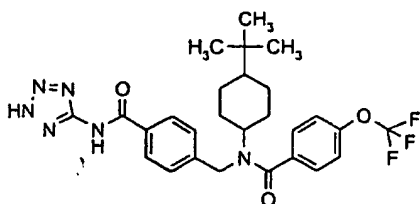


20

$^1\text{H}$  NMR (DMSO):  $\delta$  8.13 (d, 2H); 7.70-7.30 (m, 6H); 4.79 (s, 1H).

EXAMPLE 489 (general procedure (V))

4-[[[(4-*tert*-Butylcyclohexyl)-(4-trifluoromethoxybenzoyl)amino]methyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



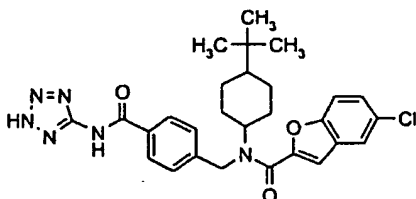
5

$^1\text{H}$  NMR (DMSO):  $\delta$  8.14 (d, 2H); 7.70-7.40 (m, 6H); 4.82 (s, 2H).

HPLC-MS (Method D):  $m/z$  = 545 ( $M+1$ ).  $R_t$  = 5.70 min.

10 EXAMPLE 490 (general procedure (V))

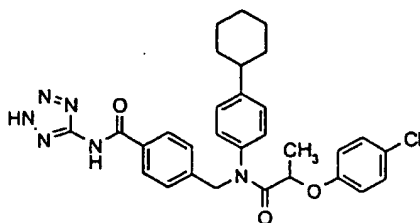
5-Chlorobenzofuran-2-carboxylic acid (4-*tert*-butylcyclohexyl)-[4-(2*H*-tetrazol-5-ylcarbamoyl)-benzyl]amide

15  $^1\text{H}$  NMR (DMSO):  $\delta$  8.13 (d, 2H); 7.90 (s, 1H); 7.54 (dd, 4H); 4.98 (s, 1H).

HPLC-MS (Method D):  $m/z$  = 535 ( $M+1$ ).  $R_t$  = 6.10 min.

EXAMPLE 491 (general procedure (V))

20 4-[[[2-(4-Chlorophenoxy)propionyl]-[4-(cyclohexylphenyl)amino]methyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



390

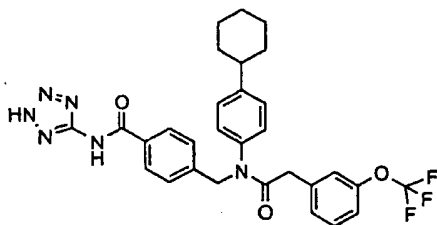
$^1\text{H}$  NMR (DMSO):  $\delta$  8.09 (d, 2H); 7.41 (d, 2H); 7.34 (d, 2H); 7.25 (dd, 4H); 6.75 (d, 2H); 5.00 (d, 2H); 4.61 (d, 1H).

HPLC-MS (Method D):  $m/z$  = 559 (M+1).  $R_t$  = 6.10 min.

5

EXAMPLE 492 (general procedure (V))

4-(((4-Cyclohexylphenyl)-[2-(3-trifluoromethoxyphenyl)acetyl]amino)methyl)-N-(2H-tetrazol-5-yl)benzamide



10

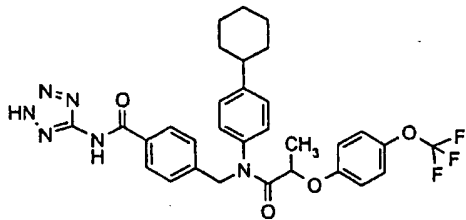
$^1\text{H}$  NMR (DMSO):  $\delta$  8.10 (d, 2H); 7.45 (m, 3H); 7.30 (m, 3H); 7.20 (m, 3H); 7.08 (s, 1H); 5.03 (s, 1H).

HPLC-MS (Method D):  $m/z$  = 579 (M+1).  $R_t$  = 6.23 min.

15

EXAMPLE 493 (general procedure (V))

4-(((4-Cyclohexylphenyl)-[2-(4-trifluoromethoxyphenoxy)propionyl]amino)methyl)-N-(2H-tetrazol-5-yl)benzamide



20

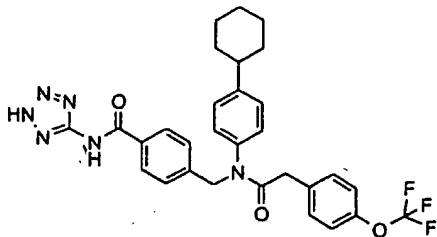
$^1\text{H}$  NMR (DMSO):  $\delta$  8.10 (d, 2H); 7.43 (d, 2H); 7.31 (d, 2H); 7.25 (s, 4H); 6.83 (d, 2H); 5.01 (dd, 2H); 4.83 (q, 1H).

HPLC-MS (Method D):  $m/z$  = 609 (M+1).  $R_t$  = 6.27 min.

25

EXAMPLE 494 (general procedure (V))

4-(((4-Cyclohexylphenyl)-[2-(4-trifluoromethoxyphenyl)acetyl]amino)methyl)-N-(2H-tetrazol-5-yl)benzamide



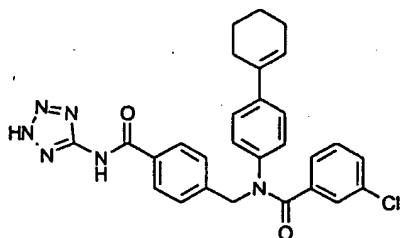
5

$^1\text{H}$  NMR (DMSO):  $\delta$  8.09 (d, 2H); 7.47 (d, 2H); 7.33-7.22 (m, 8H); 5.03 (s, 2H).

HPLC-MS (Method D):  $m/z$  = 579 ( $M+1$ ).  $R_t$  = 6.27 min.

10 EXAMPLE 495

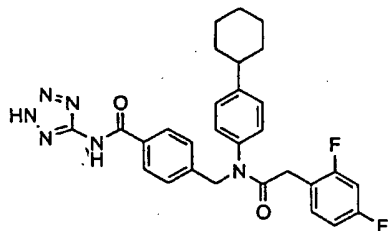
4-(((4-Cyclohex-1-enylphenyl)-(3-chlorobenzoyl)amino)methyl)-N-(2H-tetrazol-5-yl)-benzamide



15  $^1\text{H}$  NMR (DMSO):  $\delta$  12.4 (s, 1H), 8.02 (d, 2H), 7.50 (d, 2H), 7.35 (m, 1H), 7.42 (s, 1H), 7.25 (m, 4H), 7.06 (d, 2H), 6.12 (t, 1H), 5.19 (s, 2H), 2.22 (m, 2H), 2.12 (m, 2H), 1.65 (m, 2H), 1.55 (m, 2H)

**EXAMPLE 496 (general procedure (V))**

4-(((4-Cyclohexylphenyl)-[2-(2,4-difluorophenyl)acetyl]amino)methyl)-N-(2H-tetrazol-5-yl)-benzamide



5

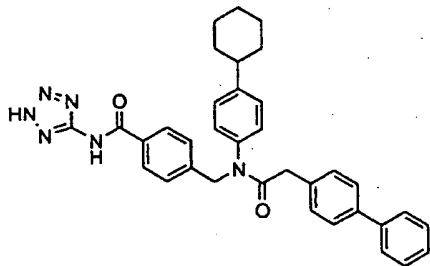
$^1\text{H}$  NMR (DMSO):  $\delta$  8.11 (d, 2H); 7.48 (d, 2H); 7.38-7.32 (m, 3H); 7.27-7.20 (m, 3H); 7.08 (t, 1H); 5.03 (s, 2H).

HPLC-MS (Method D):  $m/z$  = 531 (M+1).  $R_t$  = 5.87 min.

10

**EXAMPLE 497 (general procedure (V))**

4-(((2-Biphenyl-4-yl-acetyl)-(4-cyclohexylphenyl)amino)methyl)-N-(2H-tetrazol-5-yl)-benzamide



15

$^1\text{H}$  NMR (DMSO):  $\delta$  8.10 (d, 2H); 7.72 (d, 2H); 7.64 (d, 2H); 7.54 (t, 2H); 7.48 (d, 2H); 7.43 (t, 1H); 7.34 (d, 2H); 7.26-7.21 (m, 4H); 5.02 (s, 2H).

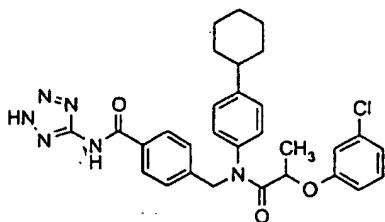
HPLC-MS (Method D):  $m/z$  = 571 (M+1).  $R_t$  = 6.50 min.

20



EXAMPLE 498 (general procedure (V))

4-[[[2-(3-Chlorophenoxy)propionyl]-(4-cyclohexylphenyl)amino]methyl]-N-(2H-tetrazol-5-yl)-benzamide



5

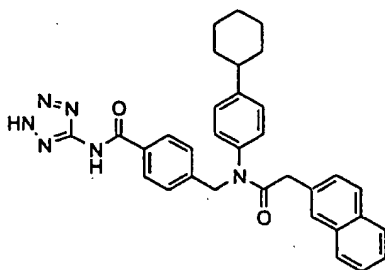
$^1\text{H}$  NMR (DMSO):  $\delta$  8.09 (d, 2H); 7.41 (d, 2H); 7.33 (t, 1H); 7.29 (d, 2H); 7.23 (d, 2H); 7.08 (d, 1H); 6.75, (m, 2H); 5.10 (d, 1H); 4.92 (d, 1H); 4.82 (q, 1H).

HPLC-MS (Method D):  $m/z$  = 559 (M+1).  $R_t$  = 6.10 min.

10

EXAMPLE 499 (general procedure (V))

4-[[[2-(2-naphth-2-ylacetyl)amino]methyl]-(4-cyclohexylphenyl)amino]methyl]-N-(2H-tetrazol-5-yl)-benzamide



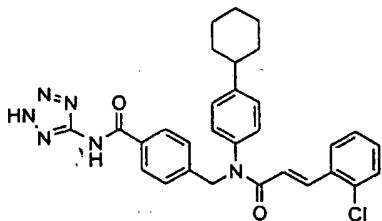
15

$^1\text{H}$  NMR (DMSO):  $\delta$  8.09 (d, 2H); 9.95 (m, 1H); 7.92-7.85 (m, 2H); 7.58-7.54 (m, 3H); 7.48 (d, 2H); 7.32 (d, 3H); 7.24 (d, 2H); 5.05 (s, 2H).

HPLC-MS (Method D):  $m/z$  = 545 (M+1).  $R_t$  = 6.23 min.

**EXAMPLE 500 (general procedure (V))**

4-([3-(2-Chlorophenyl)acryloyl]-(4-cyclohexylphenyl)amino)methyl)-N-(2H-tetrazol-5-yl)-benzamide



5

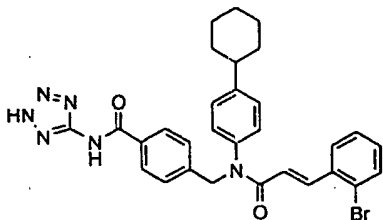
$^1\text{H}$  NMR (DMSO):  $\delta$  8.11 (d, 2H); 7.94 (d, 1H); 7.59 (d, 1H); 7.51 (d, 2H); 7.53 (t, 2H); 7.40 (d, 1H); 7.36 (d, 2H); 7.28 (d, 2H); 6.55 (d, 1H); 5.19 (s, 2H).

HPLC-MS (Method D):  $m/z$  = 541 ( $M+1$ ).  $R_t$  = 6.13 min.

10

**EXAMPLE 501 (general procedure (V))**

4-([3-(2-Bromophenyl)acryloyl]-(4-cyclohexylphenyl)amino)methyl)-N-(2H-tetrazol-5-yl)-benzamide



15

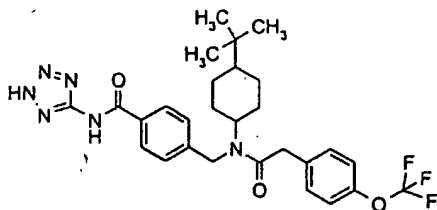
$^1\text{H}$  NMR (DMSO):  $\delta$  8.11 (d, 2H); 7.91 (d, 1H); 7.76 (d, 1H); 7.52 (d, 2H); 7.43-7.30 (m, 5H); 7.28 (d, 2H); 6.50 (d br, 1H); 5.19 (s, 2H);

HPLC-MS (Method D):  $m/z$  = 587 ( $M+1$ ).  $R_t$  = 6.23 min.

20

EXAMPLE 502 (general procedure (V))

4-(((4-*tert*-Butylcyclohexyl)-[2-(4-trifluoromethoxyphenyl)acetyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)benzamide



5

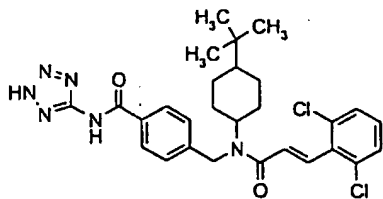
$^1\text{H}$  NMR (DMSO. Isomers 2:1):  $\delta$  8.17 + 8.07 (d, 2H); 7.55-7.45 (m, 2H); 7.45-7.30 (m, 4H); 4.80 + 4.64 (s, 2H).

HPLC-MS (Method D):  $m/z$  = 559 ( $M+1$ ).  $R_t$  = 5.97 min.

10

EXAMPLE 503 (general procedure (V))

4-(((4-*tert*-Butylcyclohexyl)-[3-(2,6-dichlorophenyl)acryloyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)benzamide



15

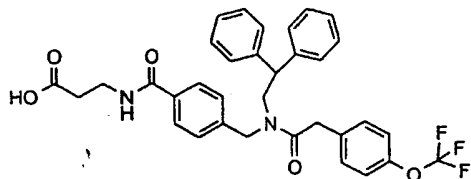
$^1\text{H}$  NMR (DMSO. Isomers 1:1):  $\delta$  8.18-8.12 (m, 2H); 7.68-7.30 (m, 7H); 6.85 (d, 1H); 4.88 (s, 1H); 4.79 (s, 1H).

HPLC-MS (Method D):  $m/z$  = 555 ( $M+1$ ).  $R_t$  = 6.13 min.

20

**EXAMPLE 504 (general procedure (V))**

3-[4-(((2,2-Diphenylethyl)-[2-(4-trifluoromethoxyphenyl)acetyl]amino)methyl)benzoylamino]-propionic acid



5

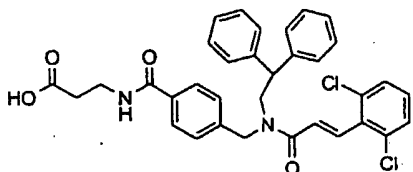
$^1\text{H}$  NMR (DMSO):  $\delta$  8.58 (t, 1H); 8.53 (t, 1H); 7.88 (d, 2H); 7.82 (d, 2H); 7.47-7.26 (m, 28 H); 7.20 (d, 2H); 7.15 (d, 2H); 4.62 (s, 2H); 4.52 (t, 2H); 4.41 (s, 2H); 4.08 (d, 2H); 4.03 (d, 2H).

HPLC-MS (Method D):  $m/z$  = 605 (M+1).  $R_t$  = 5.33 min.

10

**EXAMPLE 505 (general procedure (V))**

3-(4-(((3-(2,6-Dichlorophenyl)acryloyl)-(2,2-diphenylethyl)amino)methyl)benzoylamino)-propionic acid



15

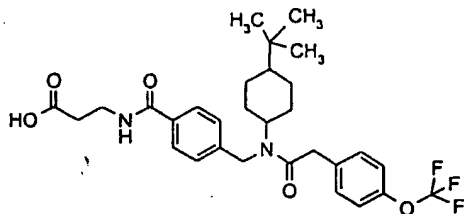
$^1\text{H}$  NMR (DMSO):  $\delta$  8.55 (t, 1H); 7.84 (dd, 2H); 7.83-7.24 (m, 16); 7.18+6.95 (d, 1H); 4.70-4.50 (m, 3H); 4.21 (t, 2H).

HPLC-MS (Method D):  $m/z$  = 601 (M+1).  $R_t$  = 5.33 min.

20

EXAMPLE 506 (general procedure (V))

3-[4-((4-*tert*-Butylcyclohexyl)-[2-(4-trifluoromethoxyphenyl)acetyl]amino)methyl]benzoyl-amino]propionic acid



5

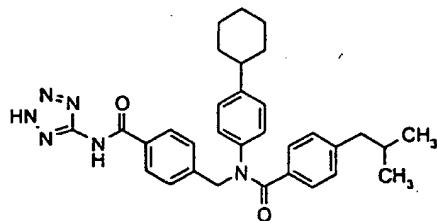
<sup>1</sup>H NMR (DMSO, Isomers): δ 8.57 + 8.51 (t, 1H); 7.90 + 7.79 (d, 2H); 7.50-7.30 (m, 6H); 4.74 + 4.60 (s, 2H).

HPLC-MS (Method D): m/z = 563 (M+1). R<sub>t</sub> = 5.73 min.

10

EXAMPLE 507 (general procedure (V))

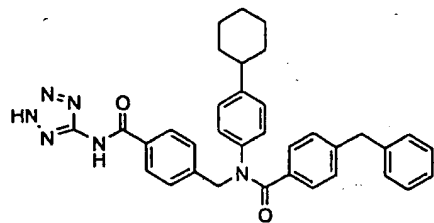
4-[[[4-(4-Cyclohexylphenyl)-[4-isobutylbenzoyl]amino]methyl]-N-(2H-tetrazol-5-yl)benzamide



15 HPLC-MS (Method D): m/z = 537 (M+1). R<sub>t</sub> = 6.57 min.

EXAMPLE 508 (general procedure (V))

4-[[[4-(4-Cyclohexylphenyl)-[4-benzylbenzoyl]amino]methyl]-N-(2H-tetrazol-5-yl)benzamide



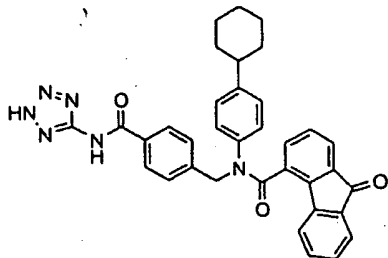
20

<sup>1</sup>H NMR (DMSO): δ 8.09 (d, 2H); 7.55 (d, 2H); 7.34-7.30 (m, 4H); 7.26-7.04 (m, 9H); 5.20 (s, 2H).

HPLC-MS (Method D):  $m/z$  = 571 ( $M+1$ ).  $R_t$  = 6.27 min.

EXAMPLE 509 (general procedure (V))

- 5 4-[[[4-(Cyclohexylphenyl)-(9-oxo-9H-fluorene-4-carbonyl)amino]methyl]-N-(2H-tetrazol-5-yl)-benzamide

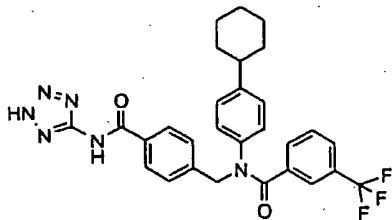


- 10  $^1\text{H}$  NMR (DMSO):  $\delta$  8.17 (d, 2H); 7.72 (d, 1H); 7.68-7.62 (m, 3H); 7.55-7.50 (m, 2H); 7.45 (d, 1H); 7.25 (t, 1H); 7.05 (d, 2H); 7.02 (d, 2H); 5.30 (s, 2H).

HPLC-MS (Method D):  $m/z$  = 583 ( $M+1$ ).  $R_t$  = 5.63 min.

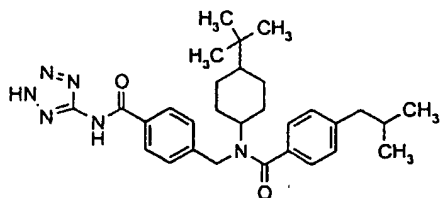
EXAMPLE 510 (general procedure (V))

- 15 4-[[[4-(Cyclohexylphenyl)-(3-trifluoromethylbenzoyl)amino]methyl]-N-(2H-tetrazol-5-yl)-benzamide



- 20  $^1\text{H}$  NMR (DMSO):  $\delta$  8.09 (d, 2H); 7.76 (d, 1H); 7.71 (d, 1H); 7.59-7.55 (m, 4H); 7.12 (s, 4H); 5.30 (s, 2H).

HPLC-MS (Method D):  $m/z$  = 549 ( $M+1$ ).  $R_t$  = 5.87 min.

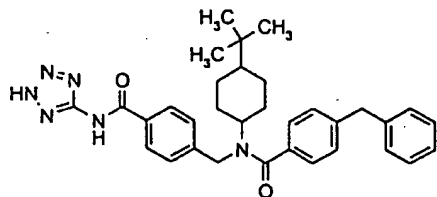
EXAMPLE 511 (general procedure (V))4-[[[(4-*tert*-Butylcyclohexyl)-(4-isobutylbenzoyl)amino]methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

5  $^1\text{H}$  NMR (DMSO):  $\delta$  8.12 (d, 2H); 7.60-7.28 (m, 6H); 4.80 (m, 2H)

HPLC-MS (Method D):  $m/z$  = 517 (M+1).  $R_t$  = 6.50 min.

EXAMPLE 512 (general procedure (V))

10 4-[[[(4-*tert*-Butylcyclohexyl)-(4-benzylbenzoyl)amino]methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

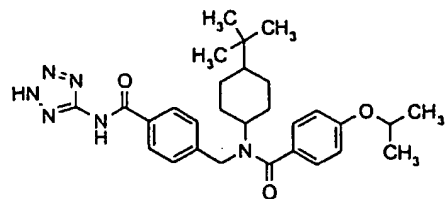


$^1\text{H}$  NMR (DMSO):  $\delta$  8.07 (d, 2H); 7.60-7.15 (m, 11H)

15 HPLC-MS (Method D):  $m/z$  = 551 (M+1).  $R_t$  = 6.23 min.

EXAMPLE 513 (general procedure (V))

4-[[[(4-*tert*-Butylcyclohexyl)-(4-isopropoxybenzoyl)amino]methyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



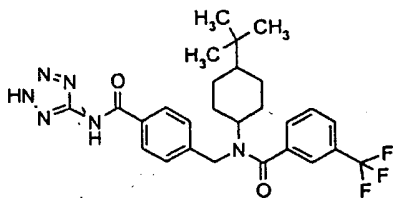
20

$^1\text{H}$  NMR (DMSO):  $\delta$  8.10 (d, 2H); 7.60-7.40 (m, 4H); 4.80-4.70 (m, 3H).

HPLC-MS (Method D):  $m/z$  = 519 (M+1).  $R_t$  = 5.87 min.

**EXAMPLE 514 (general procedure (V))**

4-(((4-*tert*-Butylcyclohexyl)-(3-trifluoromethylbenzoyl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide



5

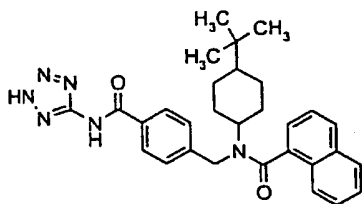
<sup>1</sup>H NMR (DMSO): δ 8.11 (d, 2H); 8.00-7.70 (m, 3H); 7.65-7.40 (m, 3H); 4.70 (s, 2H).

HPLC-MS (Method D): m/z = 529 (M+1). R<sub>t</sub> = 5.77 min.

10

**EXAMPLE 515 (general procedure (V))**

4-(((4-*tert*-Butylcyclohexyl)-(naphth-1-ylcarbonyl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide



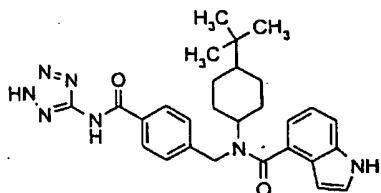
15

HPLC-MS (Method D): m/z = 511 (M+1). R<sub>t</sub> = 5.77 min.

**EXAMPLE 516 (general procedure (V))**

4-(((4-*tert*-Butylcyclohexyl)-(1*H*-indol-4-ylcarbonyl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide

20



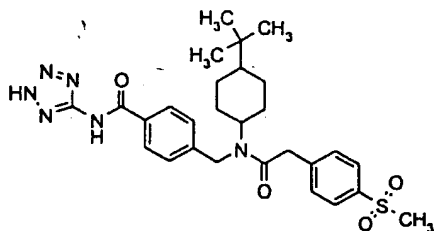
<sup>1</sup>H NMR (DMSO): δ 8.20-8.05 (m, 2H); 7.70-7.60 (m, 1H); 7.60-7.45 (m, 3H); 7.28-7.12 (m, 1H); 7.08 (d, 1H); 6.40 (m, 1H); 4.70 (s br 2H).



HPLC-MS (Method D):  $m/z$  = 500 ( $M+1$ ).  $R_t$  = 5.03 min.

EXAMPLE 517 (general procedure (V))

- 5 4-(((4-*tert*-Butylcyclohexyl)-[2-(4-methylsulfonylphenyl)acetyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)benzamide



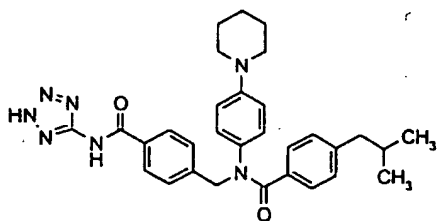
$^1\text{H}$  NMR (DMSO. Isomers 2:1):

- 10 Set 1 (minor isomer):  $\delta$  8.16 (d, 2H); 7.88 (d, 2H); 7.52 (d, 2H); 7.47 (d, 2H); 4.80 (s, 2H).  
Set 2 (major isomer):  $\delta$  8.06 (d, 2H); 7.96 (d, 2H); 7.64 (d, 2H); 7.42 (d, 2H); 4.70 (s, 2H).

HPLC-MS (Method D):  $m/z$  = 553 ( $M+1$ ).  $R_t$  = 4.83 min.

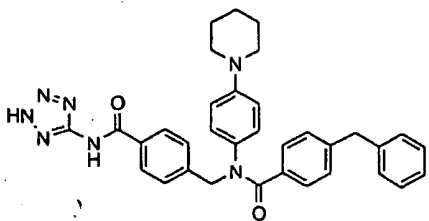
- 15 EXAMPLE 518 (general procedure (V))

4-(((4-Isobutylbenzoyl)-(4-piperidin-1-ylphenyl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)benzamide



- $^1\text{H}$  NMR (DMSO):  $\delta$  8.11 (d, 2H); 7.55 (d, 2H); 7.31 (d, 2H); 7.08 (d, 2H); 6.96 (d, 2H); 6.80 (d, 2H); 5.10 (s, 2H).
- 20

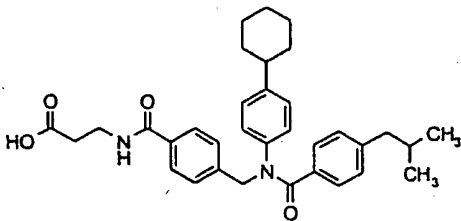
HPLC-MS (Method D):  $m/z$  = 538 ( $M+1$ ).  $R_t$  = 4.23 min.

**EXAMPLE 519 (general procedure (V))**4-[[[(4-Benzylbenzoyl)-(4-piperidin-1-ylphenyl)amino]methyl]-N-(2H-tetrazol-5-yl)benzamide

- 5  $^1\text{H}$  NMR (DMSO):  $\delta$  8.07 (d, 2H); 7.51 (d, 2H); 7.32-7.28 (m, 4H); 7.25-7.18 (m, 3H); 7.13 (d, 2H); 6.93 (d, 2H); 6.76 (d, 2H); 5.10 (s, 2H).

HPLC-MS (Method D):  $m/z$  = 572 ( $M+1$ ).  $R_t$  = 4.17 min.

10 **EXAMPLE 520 (general procedure (V))**

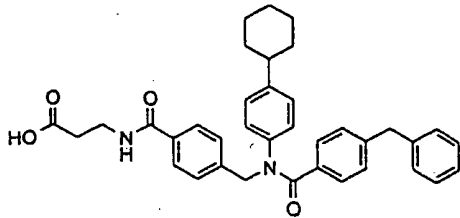
3-(4-[[[(4-Cyclohexylphenyl)-(4-isobutylbenzoyl)amino]methyl]benzoylamino]propionic acid

- 15  $^1\text{H}$  NMR (DMSO):  $\delta$  8.54 (t, 1H); 7.83 (d, 2H); 7.44 (d, 2H); 7.26 (d, 2H); 7.09-7.04 (m, 4H); 7.00 (d, 2H); 5.18 (s, 2H).

HPLC-MS (Method D):  $m/z$  = 541 ( $M+1$ ).  $R_t$  = 6.17 min.

**EXAMPLE 521 (general procedure (V))**

20 3-(4-[[[(4-Benzylbenzoyl)-(4-cyclohexylphenyl)amino]methyl]benzoylamino]propionic acid

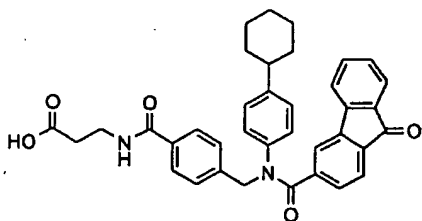


$^1\text{H}$  NMR (DMSO):  $\delta$  8.53 (t, 1H); 7.82 (d, 2H); 7.42 (d, 2H); 7.33-7.20 (m, 9H); 7.08 (d, 2H); 7.00 (d, 2H); 5.10 (s, 2H).

HPLC-MS (Method D):  $m/z$  = 575 ( $M+1$ ).  $R_t$  = 6.00 min.

5 EXAMPLE 522 (general procedure (V))

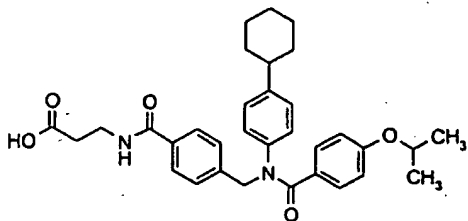
3-(4-[[[(4-Cyclohexylphenyl)-(9-oxo-9H-fluorene-3-carbonyl)amino]methyl]benzoylamino]-propionic acid



10 HPLC-MS (Method D):  $m/z$  = 587 ( $M+1$ ).  $R_t$  = 5.40 min.

EXAMPLE 523 (general procedure (V))

3-(4-[[[(4-Cyclohexylphenyl)-(4-isopropoxybenzoyl)amino]methyl]benzoylamino]propionic acid



15

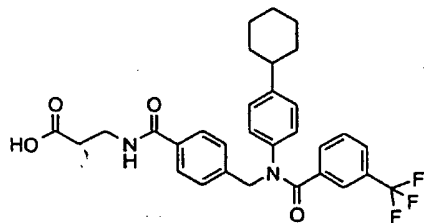
$^1\text{H}$  NMR (DMSO):  $\delta$  8.52 (t, 1H); 7.78 (d, 2H); 7.40 (d, 2H); 7.27 (d, 2H); 7.09 (d, 2H); 7.00 (d, 2H); 6.76 (d, 2H); 5.15 (s, 2H).

HPLC-MS (Method D):  $m/z$  = 543 ( $M+1$ ).  $R_t$  = 5.67 min.

20

**EXAMPLE 524 (general procedure (V))**

3-(4-((4-Cyclohexylphenyl)-(3-trifluoromethylbenzoyl)amino)methyl)benzoylamino)propionic acid



5

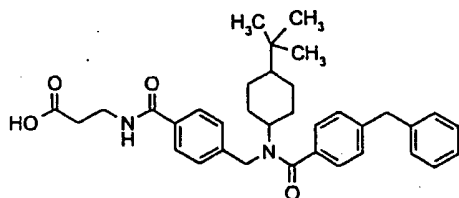
$^1\text{H}$  NMR (DMSO):  $\delta$  8.54 (t, 1H); 7.82 (d, 2H); 7.75 (d, 1H); 7.70 (d, 1H); 7.56 (t, 1H); 7.53 (s, 1H); 7.46 (d, 2H); 7.10 (d, 2H); 7.07 (d, 2H); 5.20 (s, 2H).

HPLC-MS (Method D):  $m/z$  = 553 (M+1).  $R_t$  = 5.63 min.

10

**EXAMPLE 525 (general procedure (V))**

3-(4-((4-Benzylbenzoyl)-(4-*tert*-butylcyclohexyl)amino)methyl)benzoylamino)propionic acid

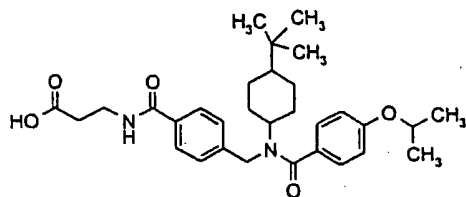


15  $^1\text{H}$  NMR (DMSO):  $\delta$  8.54 (t, 1H); 7.84 (d, 2H); 7.50-7.20 (m, 11H);

HPLC-MS (Method D):  $m/z$  = 555 (M+1).  $R_t$  = 6.00 min.

**EXAMPLE 526 (general procedure (V))**

20 3-(4-((4-*tert*-Butylcyclohexyl)-(4-isopropoxybenzoyl)amino)methyl)benzoylamino)propionic acid

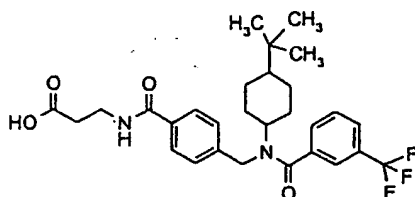


<sup>1</sup>H NMR (DMSO):  $\delta$  8.52 (t, 1H); 7.82 (d, 2H); 7.45-7.37 (m, 4H); 7.07-6.97 (m, 2H).

HPLC-MS (Method D):  $m/z$  = 523 (M+1).  $R_t$  = 5.60 min.

5 EXAMPLE 527 (general procedure (V))

3-(4-((4-*tert*-Butylcyclohexyl)-(3-trifluoromethylbenzoyl)amino)methyl)benzoylamino)propionic acid

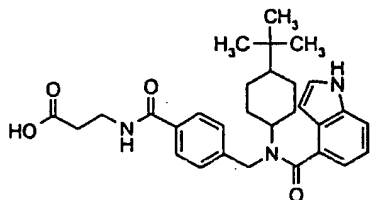


10 <sup>1</sup>H NMR (DMSO):  $\delta$  8.54 (s, 1H); 8.00-7.70 (m, 6H); 7.60-7.30 (m, 2H); 4.77 (s, 2H).

HPLC-MS (Method D):  $m/z$  = 533 (M+1).  $R_t$  = 5.53 min.

EXAMPLE 528 (general procedure (V))

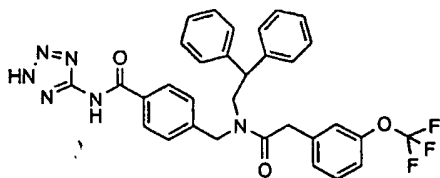
15 3-(4-((4-*tert*-Butylcyclohexyl)-(1H-indole-4-carbonyl)amino)methyl)benzoylamino)propionic acid



HPLC-MS (Method D):  $m/z$  = 504 (M+1).  $R_t$  = 5.00 min.

EXAMPLE 529 (general procedure (V))

4-(((2,2-Diphenylethyl)-[2-(3-trifluoromethoxyphenyl)acetyl]amino)methyl)-N-(2H-tetrazol-5-yl)benzamide



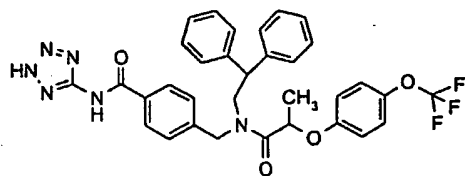
5

HPLC-MS (Method D):  $m/z$  = 601 ( $M+1$ ).  $R_t$  = 5.60 min.

EXAMPLE 530 (general procedure (V))

4-(((2,2-Diphenylethyl)-[2-(4-trifluoromethoxyphenoxy)propionyl]amino)methyl)-N-(2H-tetrazol-5-yl)benzamide

10



$^1\text{H}$  NMR (DMSO):  $\delta$  8.15 (d, 1H); 8.08 (d, 1H); 7.50-7.20 (m, 12H); 6.74 (d, 1H); 6.64 (d, 1H); 5.27 (q, 1H); 5.16 (q, 1H); 4.80 (d, 1H); (4.68 (d, 1H); 4.60-4.49 (m, 2H);

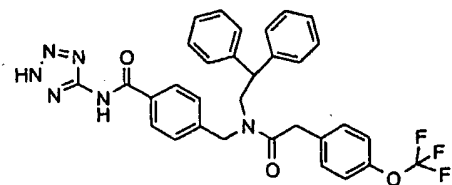
15

HPLC-MS (Method D):  $m/z$  = 631 ( $M+1$ ).  $R_t$  = 5.63 min.

EXAMPLE 531 (general procedure (V))

4-(((2,2-Diphenylethyl)-[2-(4-trifluoromethoxyphenyl)acetyl]amino)methyl)-N-(2H-tetrazol-5-yl)benzamide

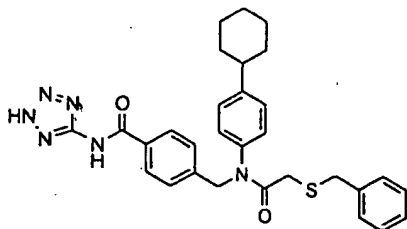
20



$^1\text{H}$  NMR (DMSO):  $\delta$  8.13 (d, 1H); 8.08 (d, 1H); 7.50-7.28 (m, 14); 7.20 (d, 1H); 7.14 (d, 1H); 4.65 (s, 1H); 4.55 (t, 1H).

EXAMPLE 532 (general procedure (V))

4-[[[(2-Benzylsulfanylacetyl)-(4-cyclohexylphenyl)amino]methyl]-N-(2H-tetrazol-5-yl)-benzamide

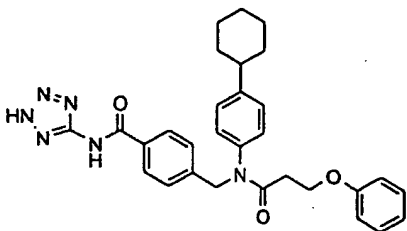


5

HPLC-MS (Method D):  $m/z$  = 541 ( $M+1$ ).  $R_t$  = 6.03 min.

EXAMPLE 533 (general procedure (V))

10 4-[[[(4-Cyclohexylphenyl)-(3-phenoxypropionyl)amino]methyl]-N-(2H-tetrazol-5-yl)benzamide



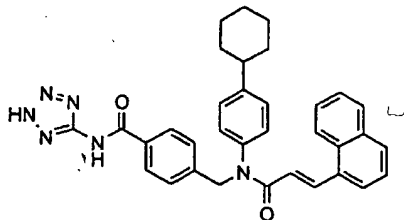
$^1\text{H}$  NMR (DMSO):  $\delta$  8.11 (d, 2H); 7.51 (d, 2H); 7.39-7.30 (m, 3H); 7.26 (d, 2H); 7.03-6.97 (m, 4H); 5.20 (s, 2H); 4.25 (t, 2H).

15

HPLC-MS (Method D):  $m/z$  = 525 ( $M+1$ ).  $R_t$  = 5.90 min.

EXAMPLE 534 (general procedure (V))

4-[[[(4-Cyclohexylphenyl)-(3-naphthalen-1-ylacryloyl)amino]methyl]-N-(2H-tetrazol-5-yl)-benzamide

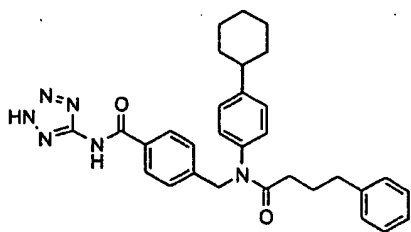


5

HPLC-MS (Method D):  $m/z$  = 557 ( $M+1$ ).  $R_t$  = 6.50 min.

EXAMPLE 535 (general procedure (V))

4-[[[(4-Cyclohexylphenyl)-(4-phenylbutyryl)amino]methyl]-N-(2H-tetrazol-5-yl)benzamide

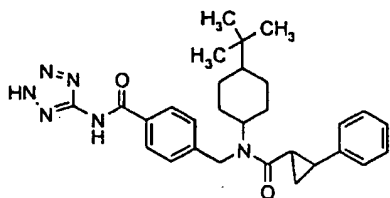


10

HPLC-MS (Method D):  $m/z$  = 523 ( $M+1$ ).  $R_t$  = 6.13 min.

EXAMPLE 536 (general procedure (V))

15 4-[[[(4-tert-Butylcyclohexyl)-(2-phenylcyclopropanecarbonyl)amino]methyl]-N-(2H-tetrazol-5-yl)benzamide



20

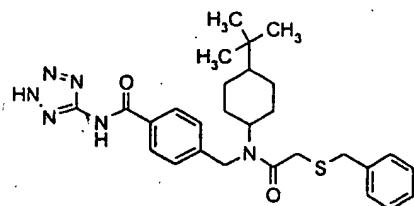
$^1\text{H}$  NMR (DMSO):  $\delta$  8.09 (d, 2H); 8.04 (d, 2H); 7.44 (d, 4H); 7.40-7.10 (m, 8H); 7.01 (d, 2H); 4.92 (d, 1H); 4.77 (d, 1H); 4.72 (d, 1H); 4.68 (d, 1H); 4.44 (t, 1H); 4.13 (t, 1H).

HPLC-MS (Method D):  $m/z$  = 501 ( $M+1$ ).  $R_t$  = 5.77 min.



**EXAMPLE 537 (general procedure (V))**

4-(((2-Benzylsulfanylacetyl)-(4-*tert*-butylcyclohexyl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide

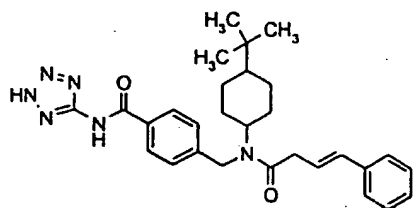


5

HPLC-MS (Method D):  $m/z$  = 521 ( $M+1$ ).  $R_t$  = 5.87 min.

**EXAMPLE 538 (general procedure (V))**

10 4-(((4-*tert*-Butylcyclohexyl)-(4-phenylbut-3-enoyl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide

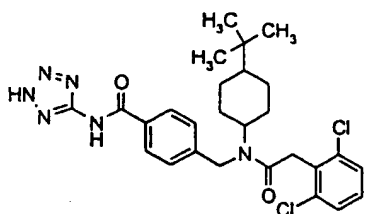


HPLC-MS (Method D):  $m/z$  = 501 ( $M+1$ ).  $R_t$  = 5.83 min.

15

**EXAMPLE 539 (general procedure (V))**

4-(((4-*tert*-Butylcyclohexyl)-[2-(2,6-dichlorophenyl)acetyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide



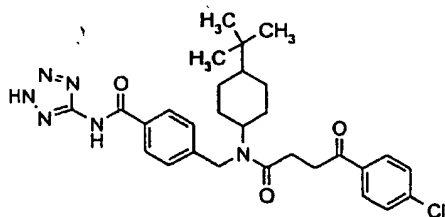
20

$^1\text{H}$  NMR (DMSO) (molecule exists as isomers 1:2): Minor isomer:  $\delta$  8.22 (d, 2H); 4.94 (s, 2H); 3.96 (s, 2H). Major isomer:  $\delta$  8.10 (d, 2H); 4.68 (s, 2H); 4.30 (s, 2H). Both isomers:  $\delta$  7.70-7.30 (m).

HPLC-MS (Method D):  $m/z = 543$  ( $M+1$ ).  $R_t = 6.20$  min.

EXAMPLE 540 (general procedure (V))

5 4-(((4-*tert*-Butylcyclohexyl)-[4-(4-chlorophenyl)-4-oxobutyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)benzamide

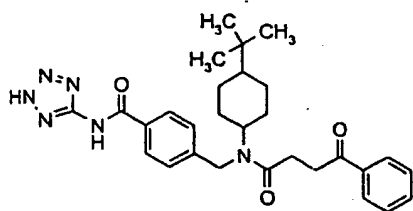


HPLC-MS (Method D):  $m/z = 551$  ( $M+1$ ).  $R_t = 5.93$  min.

10

EXAMPLE 541 (general procedure (V))

4-(((4-*tert*-Butylcyclohexyl)-[4-oxo-4-phenylbutyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide

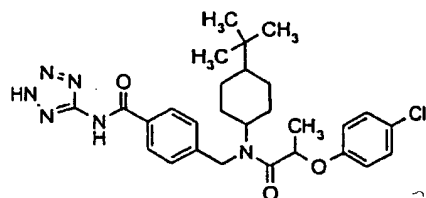


15

HPLC-MS (Method D):  $m/z = 515$  ( $M+1$ ).  $R_t = 5.60$  min.

EXAMPLE 542 (general procedure (V))

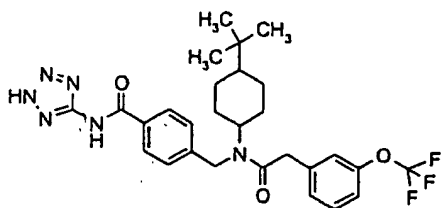
20 4-(((4-*tert*-Butylcyclohexyl)-[2-(4-chlorophenoxy)propionyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide



HPLC-MS (Method D):  $m/z = 539$  ( $M+1$ ).  $R_t = 5.97$  min.

EXAMPLE 543 (general procedure (V))

4-(((4-*tert*-Butylcyclohexyl)-[2-(3-trifluoromethoxyphenyl)acetyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)benzamide



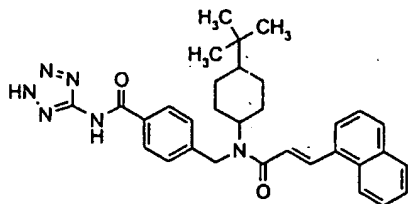
5

<sup>1</sup>H NMR (DMSO) (isomers): δ 8.18-8.05 (two d, 2H); 7.60-7.15 (m, 6H); 4.90-4.60 (two s, 2H).

10 HPLC-MS (Method D): *m/z* = 559 (*M*+1). *R*<sub>t</sub> = 6.03 min.

EXAMPLE 544 (general procedure (V))

4-(((4-*tert*-Butylcyclohexyl)-[3-naphthalen-1-yl-acryloyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide

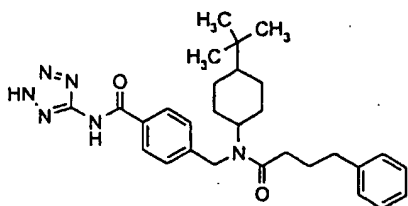


15

HPLC-MS (Method D): *m/z* = 537 (*M*+1). *R*<sub>t</sub> = 6.23 min.

EXAMPLE 545 (general procedure (V))

20 4-([4-*tert*-Butylcyclohexyl)-(4-phenylbutyryl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)benzamide

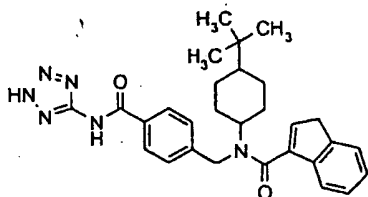


<sup>1</sup>H NMR (DMSO) (isomers): δ 8.15, 8.11 (d, 2H); 7.45-7.15 (m, 7H); 4.68, 4.65 (s, 2H).

HPLC-MS (Method D):  $m/z$  = 503 ( $M+1$ ).  $R_t$  = 5.97 min.

EXAMPLE 546 (general procedure (V))

- 5 4-(((4-*tert*-Butylcyclohexyl)-(3*H*-indene-1-carbonyl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide

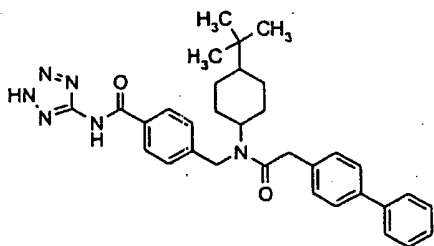


HPLC-MS (Method D):  $m/z$  = 499 ( $M+1$ ).  $R_t$  = 5.67 min.

10

EXAMPLE 547 (general procedure (V))

- 4-(((2-Biphenyl-4-ylacetyl)-(4-*tert*-butylcyclohexyl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide

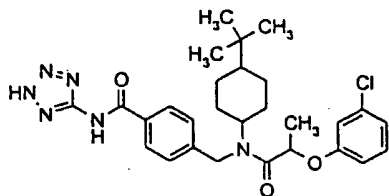


15

HPLC-MS (Method D):  $m/z$  = 551 ( $M+1$ ).  $R_t$  = 6.27 min.

EXAMPLE 548 (general procedure (V))

- 20 4-(((4-*tert*-Butylcyclohexyl)-[2-(3-chlorophenoxy)propionyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide



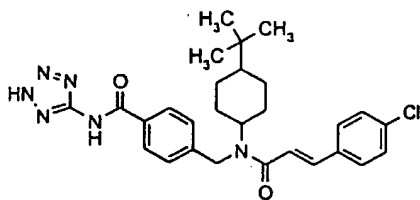
$^1\text{H}$  NMR (DMSO):  $\delta$  8.05 (d, 2H); 7.44 (t, 1H); 7.34 (d, 2H); 7.13 (d, 1H); 7.10 (s, 1H); 7.01 (d, 1H); 5.70 (q, 1H); 4.60-4.70 (dd, 2H).

HPLC-MS (Method D):  $m/z$  = 539 ( $M+1$ ).  $R_t$  = 5.97 min.

5

EXAMPLE 549 (general procedure (V))

4-(((4-*tert*-Butylcyclohexyl)-[3-(4-chlorophenyl)acroyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide



10

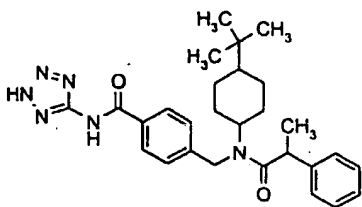
$^1\text{H}$  NMR (DMSO) (isomers):  $\delta$  8.15 (d); 8.11(d); 7.90 (d); .7.70-7.62 (m); 7.58 (d); 7.55-7.42 (m); 7.03 (d); 5.15 (s); 5.00 (s).

HPLC-MS (Method D):  $m/z$  = 521 ( $M+1$ ).  $R_t$  = 6.07 min.

15

EXAMPLE 550 (general procedure (V))

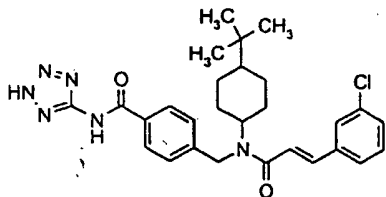
4-(((4-*tert*-Butylcyclohexyl)-(2-phenylpropionyl)amino)methyl)-*N*-(2*H*-tetrazol-5-yl)benzamide



20 HPLC-MS (Method D):  $m/z$  = 489 ( $M+1$ ).  $R_t$  = 5.83 min.

**EXAMPLE 551 (general procedure (V))**

4-(((4-*tert*-Butylcyclohexyl)-[3-(3-chlorophenyl)acryloyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)-benzamide



5

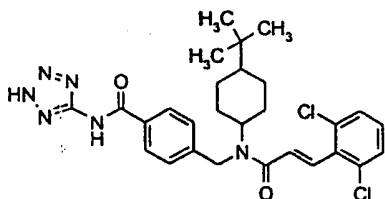
$^1\text{H}$  NMR (DMSO) (isomers):  $\delta$  8.15 (d) 8.11 8(d) 8.00 (s); 7.85-7.75 (m); 7.70-7.40 (m); 7.11 (d); 5.05 (s); 4.85 (s).

HPLC-MS (Method D):  $m/z$  = 521 ( $M+1$ ).  $R_t$  = 6.03 min.

10

**EXAMPLE 552 (general procedure (V))**

4-(((4-*tert*-Butylcyclohexyl)-[3-(2,6-dichlorophenyl)acryloyl]amino)methyl)-*N*-(2*H*-tetrazol-5-yl)benzamide



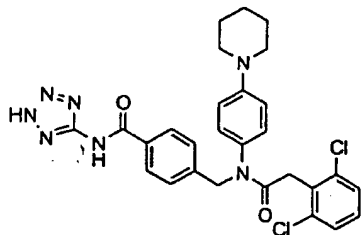
15

$^1\text{H}$  NMR (DMSO):  $\delta$  8.16 (d); 8.13 (d); 7.70-7.30 (m); 6.84 (d)

HPLC-MS (Method D):  $m/z$  = 555 ( $M+1$ ).  $R_t$  = 6.23 min.

EXAMPLE 553 (general procedure (V))

4-([2-(2,6-Dichlorophenyl)acetyl]-(4-piperidin-1-ylphenyl)amino)methyl)-N-(2H-tetrazol-5-yl)-benzamide



5

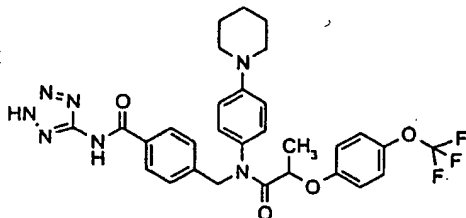
$^1\text{H}$  NMR (DMSO):  $\delta$  8.13 (d, 2H); 7.48 (d, 2H); 7.41-7.36 (m, 2H); 7.34-7.30 (m, 3H); 7.05 (d, 2H); 6.93 (d, 2H); 5.00 (s, 2H).

HPLC-MS (Method D):  $m/z$  = 479 ( $M+1$ ).  $R_t$  = 564 min.

10

EXAMPLE 554 (general procedure (V))

4-([(4-Piperidin-1-ylphenyl)-[2-(4-trifluoromethoxyphenoxy)propionyl]amino)methyl)-N-(2H-tetrazol-5-yl)benzamide



15

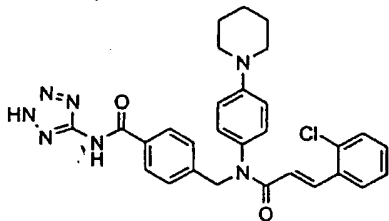
$^1\text{H}$  NMR (DMSO):  $\delta$  8.10 (d, 2H); 7.40 (d, 2H); 7.36 (d, 2H); 7.13 (d, 2H); 6.95 (d, 2H); 6.90 (d, 2H); 5.05 (d, 1H); 4.95 (d, 1H); 4.80 (q, 1H).

HPLC-MS (Method D):  $m/z$  = 610 ( $M+1$ ).  $R_t$  = 4.83 min.

20

**EXAMPLE 555 (general procedure (V))**

4-([3-(2-Chlorophenyl)acryloyl]-(4-piperidin-1-ylphenyl)amino)methyl)-N-(2H-tetrazol-5-yl)-benzamide



5

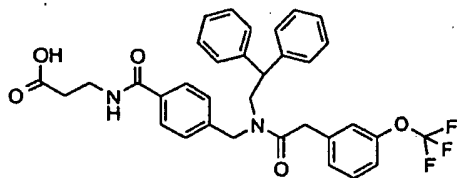
$^1\text{H}$  NMR (DMSO):  $\delta$  8.13 (d, 2H); 7.95 (d, 1H); 7.60 (d, 1H); 7.54-7.45 (m, 5H); 7.15 (d, 2H); 7.01 (d, 2H); 6.58 (d, 1H); 5.13 (s, 2H).

HPLC-MS (Method D):  $m/z$  = 542 ( $M+1$ ).  $R_t$  = 4.37 min.

10

**EXAMPLE 556 (general procedure (V))**

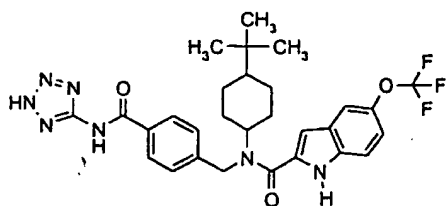
4-((2,2-Diphenylethyl)-[2-(3-trifluoromethoxyphenyl)acetyl]amino)methyl)-N-(2H-tetrazol-5-yl)benzamide





EXAMPLE 557 (general procedure (V))

5-Trifluoromethoxy-1H-indole-2-carboxylic acid (4-tert-butylcyclohexyl)-[4-(2H-tetrazol-5-ylcarbamoyl)benzyl]amide



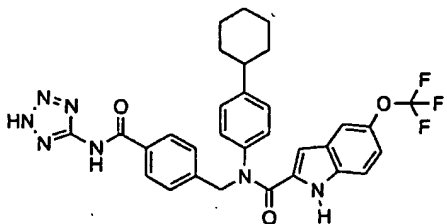
5

HPLC-MS (Method C):  $m/z = 584$  ( $M+1$ ),  $R_t = 8.07$  min.

EXAMPLE 558 (general procedure (V))

5-Trifluoromethoxy-1H-indole-2-carboxylic acid (4-cyclohexylphenyl)-[4-(2H-tetrazol-5-ylcarbamoyl)benzyl]amide

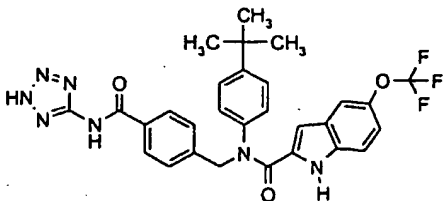
10



HPLC-MS (Method B):  $m/z = 604$  ( $M+1$ ),  $R_t = 8.33$  min.

15 EXAMPLE 559 (general procedure (V))

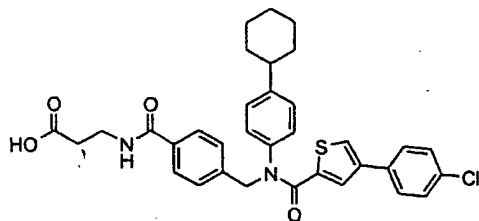
5-Trifluoromethoxy-1H-indole-2-carboxylic acid (4-tert-butylphenyl)-[4-(2H-tetrazol-5-ylcarbamoyl)benzyl]amide



20 HPLC-MS (Method B):  $m/z = 578$  ( $M+1$ ),  $R_t = 7.78$  min.

EXAMPLE 560 (general procedure (V))

3-(4-[[[4-(4-Chlorophenyl)thiophene-2-carbonyl]-(4-cyclohexylphenyl)amino]methyl]-benzoylamino)propionic acid



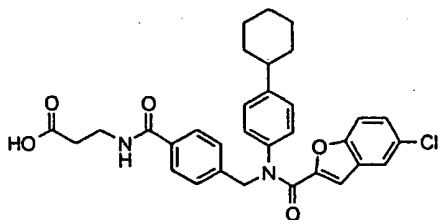
5

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  12.25 (br s, 1H); 8.50 (t, 1H); 8.05 (s, 1H); 7.75 (d, 2H); 7.42-7.30 (m, 6H); 7.28 (d, 2H); 7.18 (d, 2H); 6.62 (s, 1H); 5.09 (s, 2H); 1.80-1.65 (m, 5H); 1.40-1.15 (m, 5H).

10 HPLC-MS (Method B):  $R_t$  = 8.32 min,  $m/z$  = 601 ( $M+1$ ).

EXAMPLE 561 (general procedure (V))

3-(4-[[[5-Chlorobenzofuran-2-carbonyl]-(4-cyclohexylphenyl)amino]methyl]benzoylamino)-propionic acid



15

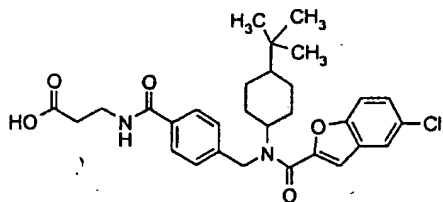
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  8.51 (t, 1H); 7.78 (d, 2H); 7.67 (s, 1H); 7.49 (d, 1H); 7.42-7.32 (m, 3H); 7.21 (d, 2H); 7.14 (d, 2H); 6.47 (s, 1H); 5.11 (s, 2H); 1.80-1.65 (m, 5H); 1.45-1.10 (m, 5H).

20

HPLC-MS (Method B):  $m/z$  = 559 ( $M+1$ ),  $R_t$  = 7.88 min.

EXAMPLE 562 (general procedure (V))

3-(4-[[[(4-*tert*-Butylcyclohexyl)-(5-chlorobenzofuran-2-carbonyl)amino]methyl]benzoylamino]-propionic acid



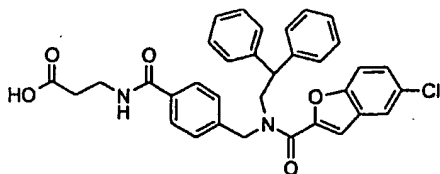
5

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  12.25 (s, 1H); 8.52 (t, 1H); 7.92-7.70(m, 4H); 7.50-7.15 (m, 4H); 4.80 (d br, 2H); 4.25-4.00 (d br, 1H); 3.50 (dd, 2H); 1.90-1.50 (m, 6H); 1.10-0.90 (m, 3H); 0.75 (s, 9H).

10 HPLC-MS (Method B):  $m/z$  = 539 (M+1).  $R_t$  = 7.85 min.

EXAMPLE 563 (general procedure (V))

3-(4-[[[(5-Chlorobenzofuran-2-carbonyl)-(2,2-diphenylethyl)amino]methyl]benzoylamino]-propionic acid



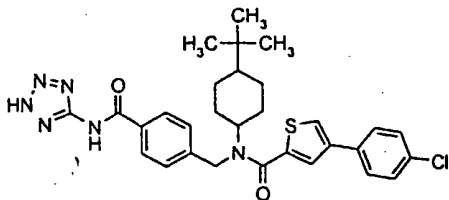
15

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  8.52 (t, 1H); 7.80 (s, 3H); 7.58 (d, 1H); 7.50-7.05 (m, 14 H); 4.65 (s, 2H); 4.50-4.05 (m, 2H).

20 HPLC-MS (Method B):  $m/z$  = 581 (M+1).  $R_t$  = 7.17 min.

**EXAMPLE 564 (general procedure (V))**

4-(4-Chlorophenyl)thiophene-2-carboxylic acid (4-*tert*-butylcyclohexyl)-[4-(2*H*-tetrazol-5-yl-carbamoyl)benzyl]amide



5

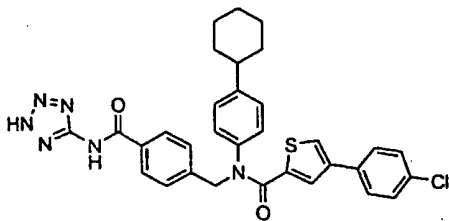
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  12.40 (s, 1H); 8.10 (m, 3H); 7.85-7.65 (m, 3H); 7.50 (m, 4H); 4.85 (br d, 2H); 4.42+4.18 (m br, 1H); 1.95-1.48 (m, 7H); 1.20-1.00 (m, 2H); 0.80 (s, 9H).

HPLC-MS (Method B):  $m/z$  = 577 (M+1).  $R_t$  = 8.37 min.

10

**EXAMPLE 565 (general procedure (V))**

4-(4-Chlorophenyl)thiophene-2-carboxylic acid (4-cyclohexylphenyl)-[4-(2*H*-tetrazol-5-yl-carbamoyl)benzyl]amide



15

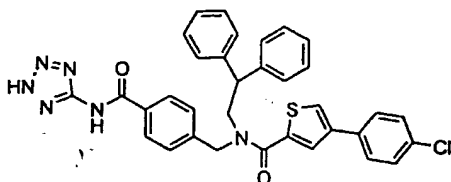
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  12.40 (s, 1H); 8.05 (d+s, 3H); 7.52 (d, 2H); 7.35 (s, 4H); 7.28 (d, 2H); 7.18 (d, 2H); 6.61 (s, 1H); 5.11 (s, 2H); 1.90-1.65 (m, 5H); 1.60-1.15 (5H).

HPLC-MS (Method B):  $m/z$  = 597 (M+1).  $R_t$  = 8.65 min.

20

EXAMPLE 566 (general procedure (V))

4-(4-Chlorophenyl)thiophene-2-carboxylic acid (2,2-diphenyl-ethyl)-[4-(2H-tetrazol-5-yl-carbamoyl)benzyl]amide



5

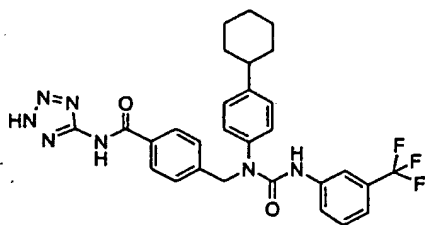
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  12.44 (s, 1H); 8.10 (s+d, 3H); 7.60 (d, 2H); 7.45-7.15 (m, 15H); 4.62 (s, 2H); 4.59 (s br, 1H); 4.28 (br s, 2H).

HPLC-MS (Method B):  $m/z$  = 619 (M+1).  $R_t$  = 7.67 min.

10

EXAMPLE 567 (general procedure (V))

4-[1-(4-Cyclohexylphenyl)-3-(3-trifluoromethylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



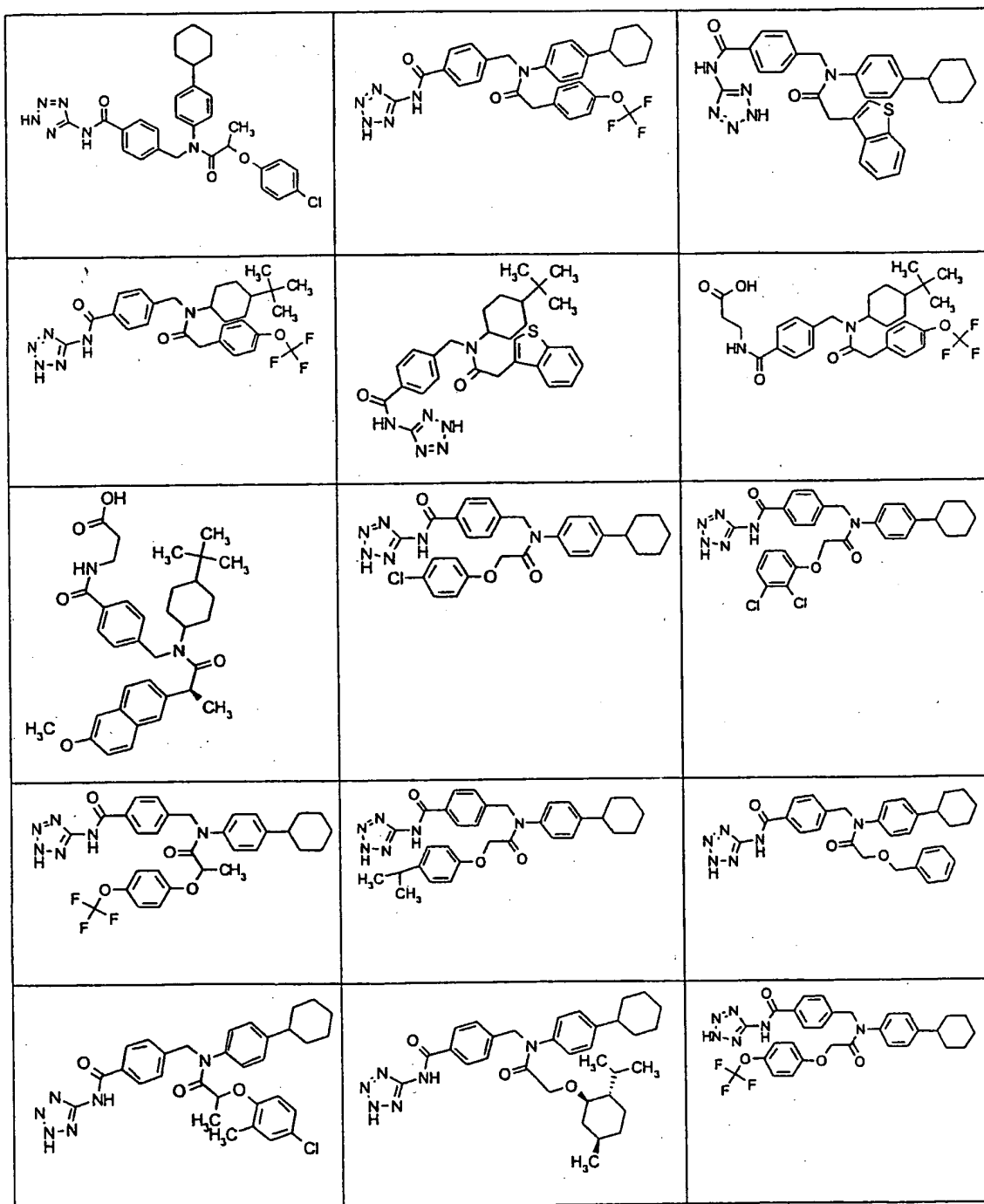
15

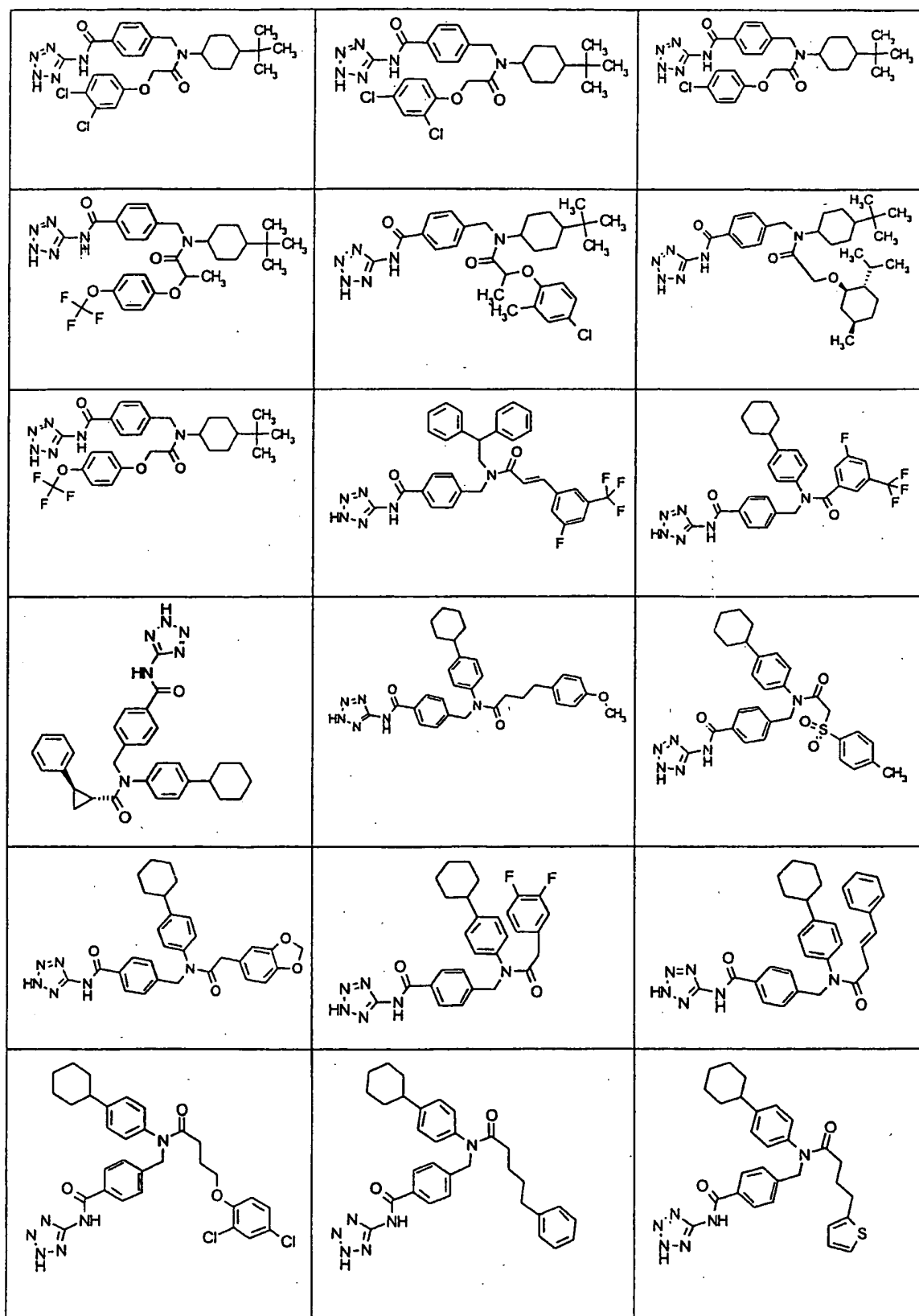
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  12.30 (s, 1H); 8.60 (s, 1H); 8.03 (d, 2H); 7.88 (s, 1H); 7.72 (d, 1H); 7.48 (m, 3H); 7.38 (d, 1H); 7.20 (s, 4H); 5.00 (s, 2H); 1.85-1.65 (m, 5H); 1.50-1.20 (m, 5H).

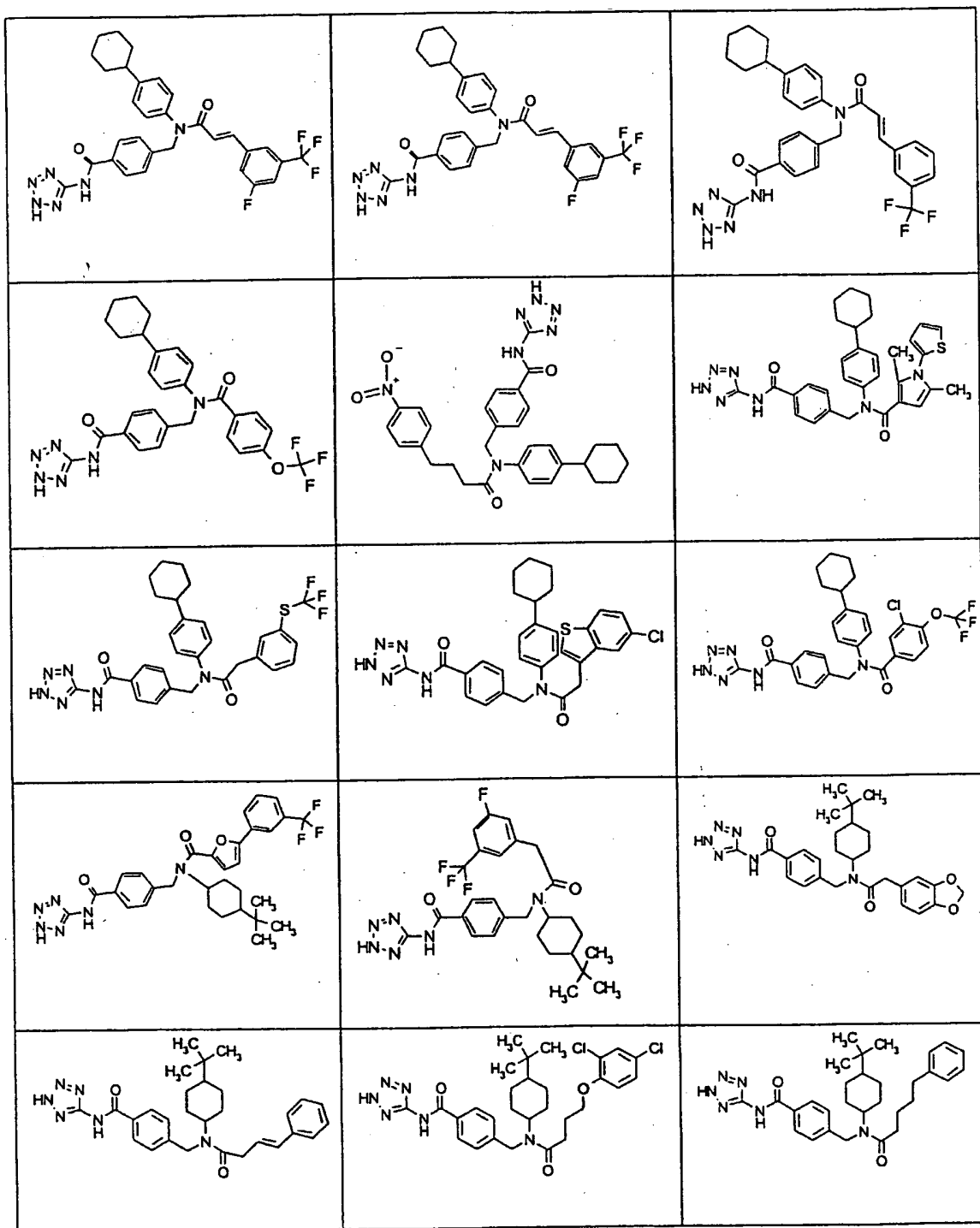
HPLC-MS (Method B):  $m/z$  = 564 (M+1),  $R_t$  = 7.85 min.

20

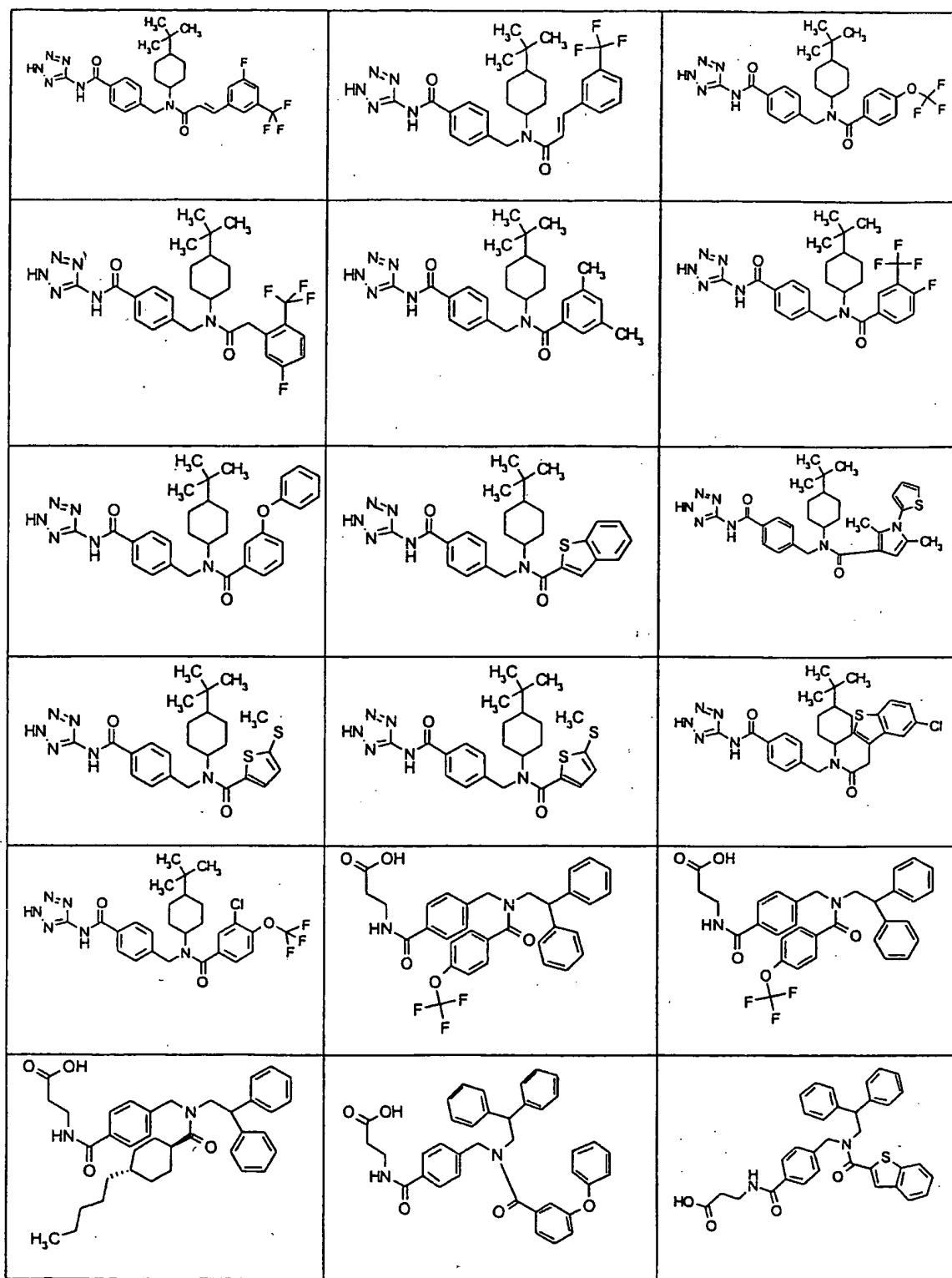
The following library of compounds was made according to general procedure (V). All of the compounds are expected to be present in the library.

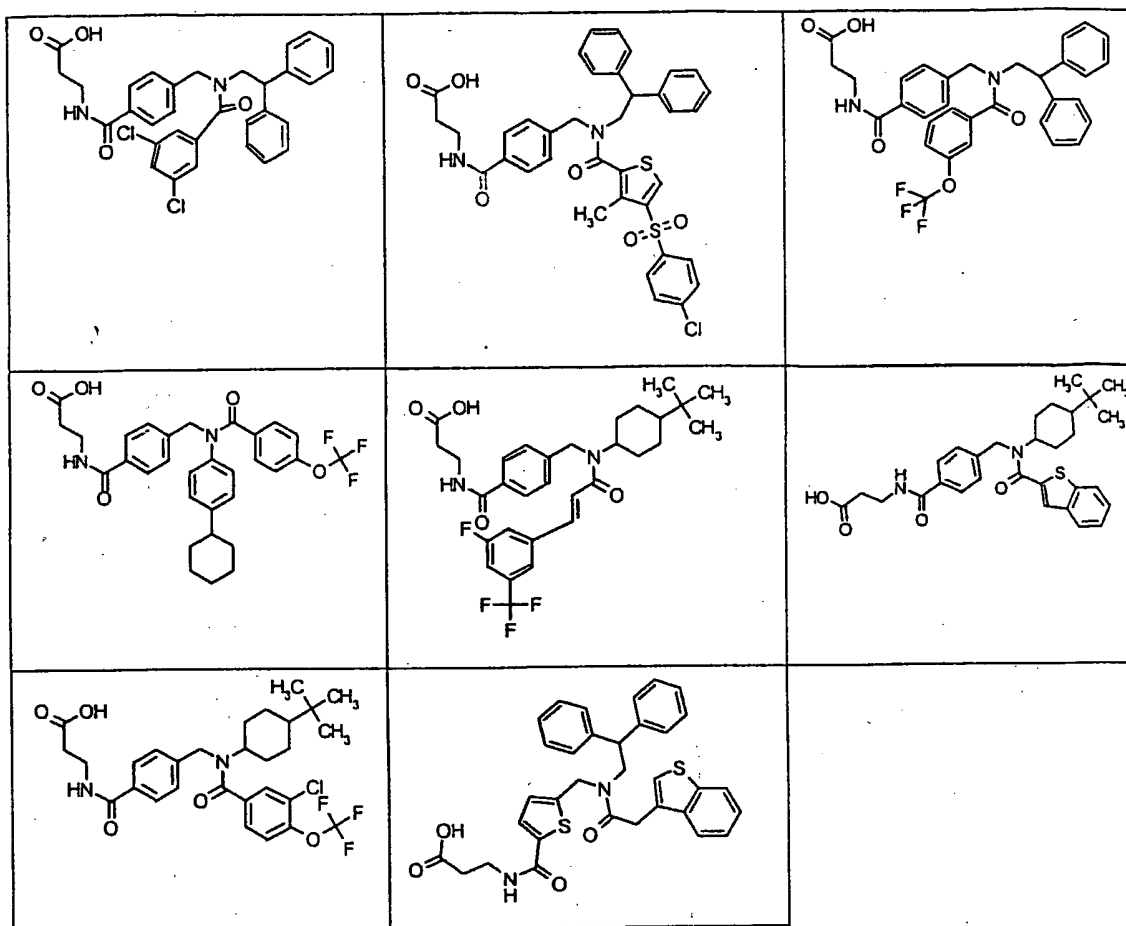




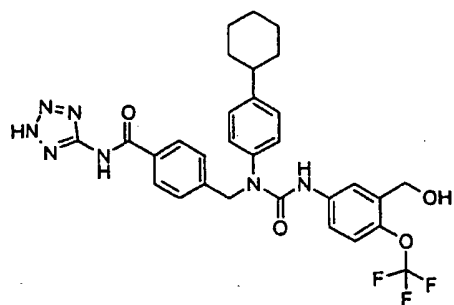






**EXAMPLE 568**

4-[1-(4-Cyclohexylphenyl)-3-(3-hydroxymethyl-4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



4-[3-[3-*tert*-Butyldimethylsilanyloxymethyl]-4-trifluoromethoxyphenyl]-1-(4-cyclohexylphenyl)-ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide (0.09 g, 0.12 mmol) (example 293) was dis-

solved in THF (2 mL) and a solution of tetrabutylammonium fluoride in THF (0.4 mL, 0.4 mmol, 1M) was added. The mixture was stirred for 6.5 hours and concentrated in vacuo. The residue was purified by column chromatography using 35 g of silica and dichloromethane and 10% ammonia in ethanol (80:20) as eluent to give 75 mg of the title compound.

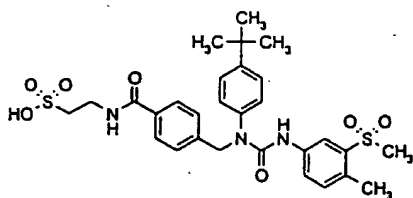
5 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.52-1.62 (6H, m), 1.68-1.83 (5H, m), 4.50 (2H, d), 4.98 (2H, s), 5.36 (1H, t), 7.16-7.22 (5H, m), 7.40 (2H, d), 7.53 (1H, dd), 7.64 (1H, d), 7.95 (2H, d), 8.44 (1H, s), 10.67 (1H, broad)

HPLC ms (method B): m/z: 610, R<sub>t</sub> = 7.34 min.

10

#### EXAMPLE 569

2-[4-[1-(4-*tert*-Butylphenyl)-3-(3-methylsulfonyl-4-methylphenyl)ureidomethyl]-benzoylamino]-ethanesulfonic acid



15

4-[1-(4-*tert*-Butylphenyl)-3-(3-methylsulfonyl-4-methylphenyl)ureidomethyl]benzoic acid (300 mg, 0.6 mmol) was dissolved in DMF (10 ml). Hydroxybenzotriazole (100 mg, 0.7 mmol), and *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (130 mg, 0.7 mmol) were added and the mixture was stirred for 30 minutes at room temperature followed by addition of  
20 2-aminoethanesulfonic acid (110 mg, 0.9 mmol) and diisopropylethylamine (120 mg, 160 μl, 1.0 mmol). After 16 hours the reaction mixture was poured into water (40 mL), pH was adjusted to acidic reaction with sodium hydrogen sulphate and the solution was concentrated in vacuo. The residue was purified by flash chromatography (20 g Silica Gel) using methanol and dichloromethane (10:90) as eluent to give 0.2 g of the title compound.

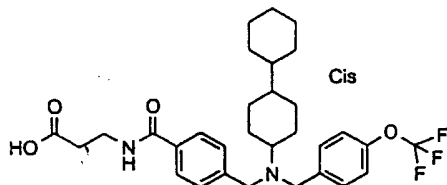
25

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.60 (s, 1H); 8.48 (t, 1H); 8.05 (s, 1H) 7.78 (d, 1H); 7.71 (d, 2H); 7.38 (d, 2H); 7.36 (d, 2H); 7.31 (d, 1H); 7.18 (d, 2H); 4.95 (s, 2H); 3.5 (q, 2H); 3.17 (s, 3H); 2.66 (t, 2H); 2.54 (s, 3H); 1.27 (s, 9H).

30 HPLC-MS (method B): m/z: 602, R<sub>t</sub> = 4.8 min.

**EXAMPLE 570**

3-(4-(((*cis*-4-Cyclohexylcyclohexyl)-(4-trifluoromethoxybenzyl)amino)methyl)benzoylamino)-propionic acid



To a solution of 4-trifluoromethoxybenzylamine (2.76 g, 14.4 mmol) in methanol (150 mL) was added 4-(4-cyclohexyl)cyclohexanone (2.60 g, 14.4 mmol) and NaBH(OAc)<sub>3</sub> (3.64 g, 17.2 mmol). The mixture was stirred for 16 hours at room temperature, and filtered by suction. The filtrate was concentrated, the residue was dissolved in ethyl acetate (150 mL), washed with NaHCO<sub>3</sub> solution (100 mL), brine (100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The *cis*- and *trans*-isomers were separated by flash chromatography. The *cis*-isomer together with a byproduct eluted with hexane, ethyl acetate (5:1) and was used without further purification and characterization in the next step. Pure *trans*-isomer was eluted with hexane, ethyl acetate (3:1).

*N*-[4-(*trans*-4-Cyclohexyl)cyclohexyl]-4-trifluoromethoxybenzylamine:

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.82- 1.17 (m, 11H), 1.59 - 1.76 (m, 7H), 1.86 (d, 2H), 2.41 (m, 1H), 3.81 (s, 2 H), 7.16 (d, 2H), 7.34 (d, 2H). MS (APCI, pos.): 356.2 (M+1).

To a solution of crude *N*-4-(*cis*-4-cyclohexylcyclohexyl)-4-trifluoromethoxybenzylamine (760 mg) in dichloromethane (10 mL) was added ethyl 3-[(4-formylbenzoyl)amino]propionate (240 mg, 1.0 mmol) and NaBH(OAc)<sub>3</sub> (240 mg, 1.1 mmol). After stirring for 16 hours at room temperature, the mixture was diluted with ethyl acetate (20 mL), washed with NaHCO<sub>3</sub> solution (10 mL), and brine (10 mL), dried (MgSO<sub>4</sub>), and concentrated. Flash chromatography (hexane, ethyl acetate, 3:1) afforded *N*-[4-(((*cis*-4-cyclohexyl)cyclohexyl)-[4-(trifluoromethoxy)benzyl]amino)methyl)benzoyl]-β-alanine ethyl ester (226 mg).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.82 - 1.86 (m, 23H), 2.49 (m, 1H), 2.64 (t, 2H), 3.62 (s, 2H), 3.66 (s, 2H), 3.70 (q, 2H), 4.15 (q, 2 H), 6.84 (t, 1H), 7.12 (d, 2H), 7.35 (d, 2H), 7.40 (d, 2H), 7.68 (d, 2H).

MS (APCI, pos.): 589.2 (M+1)

The above ester was dissolved in THF (10 mL), and 1M LiOH (0.5 mL) was added. After stirring at room temperature for 16 hours, the solution was acidified with 1N HCl to pH = 4, and concentrated. The residue was dissolved in acetone (15 mL), filtered by suction, and the filtrate was concentrated. The title compound was purified by HPLC.

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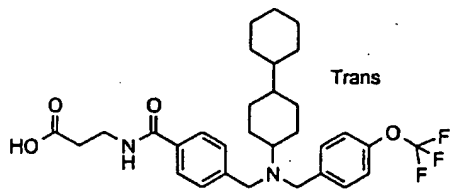
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.71-1.87 (m, 20H), 2.37 (t, 2 H), 3.40 (t, 2H), 3.61 (s, 2H), 3.63 (s, 2H), 7.20 (d, 2H), 7.39 (d, 2 H), 7.44 (d, 2H), 7.67 (d, 2H), 8.53 (t, 1H).

MS (APCI, pos.): 561.3 (M+1).

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#### EXAMPLE 571

3-(4-[[[(trans-4-Cyclohexylcyclohexyl)-(4-trifluoromethoxybenzyl)amino]methyl]benzoyl-amino]propionic acid



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To a solution of *N*-[4-(*trans*-4-cyclohexylcyclohexyl)]-4-trifluoromethoxybenzylamine (149 mg, 0.42 mmol) in dichloromethane (10 mL) was added ethyl 3-[(4-formylbenzoyl) amino] propionate (104 mg, 0.42 mmol) and NaBH(OAc)<sub>3</sub> (132 mg, 0.62 mmol). After stirring for 16 hours at room temp. additional aldehyde (100 mg) and NaBH(OAc)<sub>3</sub> (132 mg) were added. After stirring for 72 hours at room temp., the mixture was diluted with ethyl acetate (20 mL), washed with NaHCO<sub>3</sub> solution (10 mL), brine (10 mL), dried (MgSO<sub>4</sub>), and concentrated. Flash chromatography (hexane, ethyl acetate, 3:1) provided the title compound (74.2 mg).

$^1\text{H}$  NMR (CDCl<sub>3</sub>):  $\delta$  0.82 - 1.77 (m, 21H), 1.89 (d, 2H), 2.38 (tt, 1 H), 2.64 (t, 2H), 3.60 (s, 2H), 3.64 (s, 2H), 3.72 (q, 2H), 4.16 (q, 2H), 6.82 (t, 1H), 7.12 (d, 2H), 7.35 (d, 2H), 7.40 (d, 2H), 7.68 (d, 2H).

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MS (APCI, pos.): 589.2 (M+1)

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The above ester was dissolved in THF, and excess 1M LiOH was added. After stirring at room temperature for 16 hours, the solution was acidified with 1N HCl to pH=4, and concen-

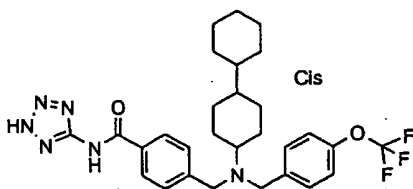
trated. The residue was dissolved in acetone (15 mL), filtered by suction, and the filtrate was concentrated. On addition of ethyl ether the title compound crystallized. Yield: 65 mg.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, D<sub>2</sub>O, NaOD): δ 0.80-1.82 (m, 20H), 2.13 (t, 2 H), 2.60 (t, 1H), 3.33 (t, 2H), 3.55 (s, 2H), 3.57 (s, 2H), 7.22 (d, 2H), 7.36 (d, 2H), 7.42 (d, 2H), 7.68 (d, 2H).

MS (APCI, pos.): 561.2 (M+1).

#### EXAMPLE 572

10 4-(((4-cis-Cyclohexylcyclohexyl)-[4-(trifluoromethoxy)benzyl]amino)methyl)-N-(2H-tetrazol-5-yl)benzamide



To a solution of crude *cis-N-4-(4-cyclohexylcyclohexyl)-4-trifluoromethoxybenzylamine* (1.70g) in dichloromethane (10 mL) was added methyl 4-formylbenzoate (500 mg, 3.04 mmol) and NaBH(OAc)<sub>3</sub> (500 mg, 2.36 mmol). After stirring for 16 hours at room temperature, the mixture was diluted with dichloromethane (20 mL), washed with NaHCO<sub>3</sub> solution (2 x 20 mL) and brine (20 mL), dried (MgSO<sub>4</sub>), and concentrated. Flash chromatography (hexane, ethyl acetate, 9:1) provided methyl 4-(((4-cis-cyclohexylcyclohexyl)-[4-(trifluoromethoxy)-benzyl]amino)methyl)benzoate (836 mg).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.77 - 1.85 (m, 20H), 2.50 (m, 1H), 3.62 (s, 2 H), 3.68 (s, 2 H), 3.90 (s, 3H), 7.11 (d, 2H), 7.35 (d, 2 H), 7.40 (d, 2H), 7.95 (d, 2H).

25 MS (APCI, pos.): 504.2 (M+1).

The above ester (836 mg, 1.66 mmol) was dissolved in THF (10 mL) and methanol (10 mL), and 1M KOH (4 mL) was added. The mixture was refluxed for 5h, acidified with 1N HCl to pH = 4, and concentrated. The residue was dissolved in ethyl acetate (20 mL), washed with brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue crystallized from hexanes and ethyl acetate. Yield: 786 mg of 4-(((4-cis-cyclohexylcyclohexyl)-[4-(trifluoromethoxy)benzyl]-amino)methyl)benzoic acid as a white solid.

<sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 0.70 (m, 2 H), 1.13- 1.22 (m, 8H), 1.61-2.00 (m, 10H), 3.38 (t, 1H), 4.26 (m, 2H), 4.54 (m, 2H), 7.34 (d, 2H), 7.67 (d, 2H), 7.75 (d, 2H), 7.87 (d, 2H). MS (APCI, pos.): 490.2 (M+1).

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To a solution of above benzoic acid (250 mg, 0.51 mmol) in DMF (8 mL) was added diisopropylethylamine (0.18 mL, 130 mg, 0.61 mmol) and HBTU (228 mg, 0.61 mmol). After stirring for 15 min at room temperature, 5-aminotetrazole (105 mg, 1.01 mmol) was added. The mixture was stirred for 16 hours, and the solvent was evaporated. The residue was dissolved in ethyl acetate (20 mL), washed with water (2 x 10 mL), and brine (10 mL), dried (MgSO<sub>4</sub>), and concentrated. The residue was dissolved in dichloromethane. On addition of ether and hexane, the title compound crystallized. Yield: 26 mg.

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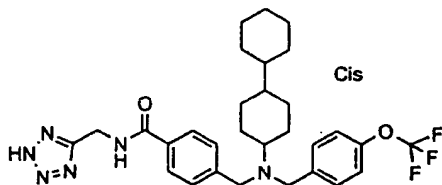
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.70 - 0.84 (m, 2H), 1.00- 1.80 (m, 18H), 2.40 (m, 1 H), 3.65 (s, 2H), 3.70 (s, 2H), 7.27 (d, 2H), 7.46 (d, 2H), 7.50 (d, 2 H), 8.01 (d, 2H).

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MS (APCI, pos.): 557.2 (M+1).

#### EXAMPLE 573

20 4-(((4-*cis*-Cyclohexyl)cyclohexyl)-[4-(trifluoromethoxy)benzyl]amino)methyl)-*N*-(2*H*-tetrazol-5-ylmethyl)benzamide



To a solution of the above 4-(((4-*cis*-cyclohexyl)cyclohexyl)-[4-(trifluoromethoxy)benzyl]-amino)methyl)benzoic acid (242 mg, 0.49 mmol) in DMF (8 mL) was added diisopropylethylamine (0.18 mL, 130 mg, 0.61 mmol) and HBTU (220 mg, 0.59 mmol). After stirring for 15 minutes at room temperature, 5-aminomethyltetrazole (58 mg, 0.59 mmol) was added. The mixture was stirred for 16 hours, and the solvent was evaporated. The residue was dissolved in ethyl acetate (20 mL), washed with water (2 x 10 mL), and brine (10 mL), dried (MgSO<sub>4</sub>), and concentrated. The residue was purified by HPLC to afford the title compound.

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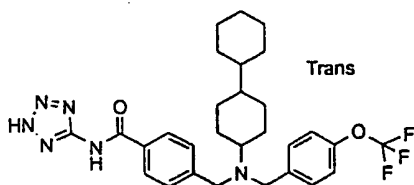
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.75 - 1.80 (m, 20H), 2.45 (m, 1H), 3.63 (s, 2H), 3.65 (s, 2H), 4.67 (d, 2H), 7.28 (d, 2H), 7.43 (d, 2H), 7.46 (d, 2H), 7.82 (d, 2H), 8.96 (t, 1H).

MS (APCI, pos.): 571.2 (M+1).

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#### EXAMPLE 574

4-(((trans-4-Cyclohexylcyclohexyl)-[4-(trifluoromethoxy)benzyl]amino)methyl)-N-(2H-tetrazol-5-yl)benzamide



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To a solution of *trans*-N-4-(4-cyclohexylcyclohexyl)-4-trifluoromethoxybenzylamine (350 mg, 0.98 mmol) in dichloromethane was added methyl 4-formylbenzoate (160 mg, 0.98 mmol) and NaBH(OAc)<sub>3</sub> (310 mg, 1.47 mmol). The mixture was stirred at room temperature for 16 hours. Additional aldehyde (160 mg) and NaBH(OAc)<sub>3</sub> (360 mg) were added. Stirring was continued for 72 hours at room temperature. The mixture was diluted with ethyl acetate (20 mL), washed with NaHCO<sub>3</sub> solution (10 mL) and brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. Flash chromatography (hexanes, ethyl acetate, 5:1) provided methyl 4-(((4-*trans*-cyclohexylcyclohexyl)-[4-(trifluoromethoxy)benzyl]amino)methyl)benzoate (290 mg).

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<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.88 - 1.31 (m, 11H), 1.59 - 1.72 (m, 7H), 1.88 (d, 2H), 2.39 (m, 1H), 3.61 (s, 2H), 3.66 (s, 2H), 3.90 (s, 3H), 7.11 (d, 2H), 7.35 (d, 2H), 7.41 (d, 2H), 7.95 (d, 2H).

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MS (APCI, pos.): 504.2 (M+1).

The above methyl benzoate (290 mg, 0.57 mmol) was dissolved in THF (5 mL) and methanol (5 mL) and 1M KOH (2 mL) were added. The mixture was refluxed for 90 minutes, acidified with 1N HCl to pH = 4, and concentrated. The residue was dissolved in ethyl acetate (20 mL), washed with brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue crystallized from hexanes, ethyl acetate to afford 4-(((4-*trans*-cyclohexylcyclohexyl)-[4-(trifluoromethoxy)benzyl]amino)methyl)benzoic acid (252 mg) as a white solid.

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<sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 0.87 - 1.36 (m, 11H), 1.59 - 1.72 (m, 7H), 1.73 (d, 2H), 2.41 (m, 1H), 3.64 (s, 4H), 4.11 (s, 1H), 7.17 (d, 2H), 7.35 (d, 2H), 7.44 (d, 2H), 7.87 (d, 2H).

MS (APCI, pos.): 490.2.2 (M+1).

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To a suspension of above benzoic acid (215 mg, 0.44 mmol) in DMF (10 mL) was added diisopropylethylamine (0.23 mL, 166 mg, 1.28 mmol) and HBTU (200 mg, 0.53 mmol). After stirring for 15 minutes at room temperature, 5-aminotetrazole (180 mg, 1.75 mmol) was added to the solution. After stirring for 16 hours, the solvent was evaporated. The residue was dissolved in ethyl acetate (30 mL), washed with water (3 x 10 mL), and brine (10 mL), dried (MgSO<sub>4</sub>), and concentrated. Flash chromatography (CHCl<sub>3</sub>, methanol, 95:5) gave 110 mg of the title compound, which was further purified by HPLC.

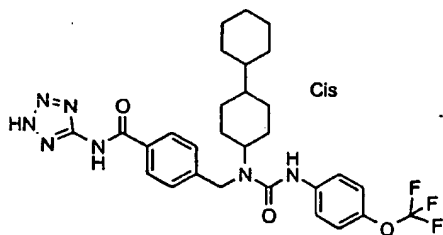
<sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 0.98 - 1.27 (m, 9H), 1.64 - 1.85 (m, 7H), 1.93 (m, 2H), 2.14 (m, 2H), 3.23 (m, 1H), 4.52 (m, 4H), 7.36 (d, 2H), 7.53 (d, 2H), 7.60 (d, 2H), 8.10 (d, 2H).

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MS (APCI, pos.): 557.3 (M+1).

#### EXAMPLE 575

20 4-[1-(4-*cis*-Cyclohexylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



To a suspension of methyl 4-(aminomethyl)benzoate hydrochloride (2.0 g, 10 mmol) (prepared according to P. M. O'Brien et al., J. Med. Chem. 37, 1994, 1810-22) in ethanol (150 mL) was added 4-(4-cyclohexyl)cyclohexanone (1.8 g, 10 mmol) and NaBH(OAc)<sub>3</sub> (2.7 g, 12 mmol). The mixture was stirred for 16 hours at room temperature, and filtered by suction. The filtrate was concentrated, and the residue was dissolved in ethyl acetate (150 mL), washed with NaHCO<sub>3</sub> solution (100 mL), brine (100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. *Cis*- and *trans*-isomers were separated by flash chromatography. The *cis*-isomer (340 mg)

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eluted with hexane, ethyl acetate, 5:1, the *trans*-isomer (338 mg) eluted with hexane, ethyl acetate, 1:1.

Methyl 4-[4-(*cis*-4-cyclohexyl)cyclohexyl]aminomethyl]benzoate:

- 5  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  0.91 - 1.75 (m, 20H), 2.75 (m, 1H), 3.82 (s, 2H), 3.91 (s, 3H), 7.41 (d, 2H), 8.00 (d, 2H).

MS (APCI, pos.): 330.2 (M+1).

- 10 Methyl 4-[4-(*trans*-4-cyclohexyl)cyclohexyl]aminomethyl]benzoate:

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  0.87 - 1.20 (m, 11H), 1.59 - 1.72 (m, 7H), 1.83 (d, 2H), 2.36 (m, 1H), 3.80 (s, 2H), 3.87 (s, 3H), 7.33 (d, 2H), 7.95 (d, 2H).

MS (APCI, pos.): 330.2 (M+1).

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To a solution of methyl 4-[4-(*cis*-4-cyclohexyl)cyclohexyl]aminomethyl]benzoate (340 mg, 1.03 mmol) in dichloromethane (8 mL) was added 4-(trifluoromethoxy)phenylisocyanate (210 mg, 1.03 mmol). After stirring for 16 hours at room temperature, the mixture was diluted with dichloromethane (10 mL), washed with 1N HCl (5 mL), brine (5 mL), dried ( $\text{MgSO}_4$ ), and concentrated. Recrystallisation from hexanes, ethyl acetate 1:1 provided 290 mg of 4-[1-(4-*cis*-cyclohexylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid methyl ester.

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$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  0.79 - 1.95 (m, 20H), 3.93 (s, 3H), 4.48 (m, 1H), 4.55 (s, 2H), 6.15 (s, 1H), 7.07 (d, 2H), 7.20 (d, 2H), 7.45 (d, 2H), 8.08 (d, 2H).

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MS (APCI, pos.): 533.2 (M+1).

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The above ester (290 mg, 0.54 mmol) was dissolved in THF (5 mL) and methanol (5 mL) and 1M KOH (2 mL) was added. The mixture was refluxed for 1 hour, acidified with 1N HCl to pH = 4, and concentrated. The residue was dissolved in ethyl acetate (20 mL), washed with brine (10 mL), dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. The residue crystallized from hexane, ethyl acetate to afford 192 mg of 4-[1-(4-*cis*-cyclohexylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid as a white solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.66 - 1.80 (m, 20H), 4.04 (m, 1H), 4.62 (s, 2H), 7.20 (d, 2H), 7.37 (d, 2H), 7.51 (d, 2H), 7.86 (d, 2H), 8.54 (s, 1H). MS (APCI, pos.): 519.1 (M+1).

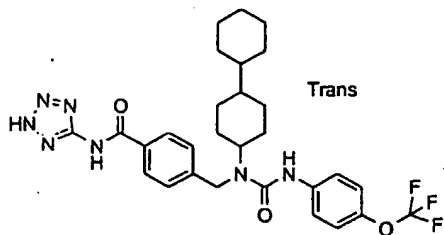
To a solution of the above benzoic acid (192 mg, 0.36 mmol) in DMF (10 mL) was added diisopropylethylamine (0.19 mL, 137 mg, 0.72 mmol) and HBTU (190 mg, 0.51 mmol). After stirring for 15 minutes at room temperature, 5-aminotetrazole (74 mg, 0.72 mmol) was added. After stirring for 16 hours, the solvent was evaporated, the residue was dissolved in ethyl acetate (20 mL), washed with water (2 x 10 mL), brine (10 mL), dried (MgSO<sub>4</sub>), and concentrated. The residue was purified by HPLC to afford the title compound.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.66 - 1.80 (m, 20H), 4.10 (m, 1H), 4.65 (s, 2H), 7.23 (d, 2H), 7.43 (d, 2H), 7.54 (d, 2H), 8.05 (d, 2H), 8.58 (s, 1H), 12.26 (s, 1H).

MS (APCI, pos.): 586.1 (M+1).

#### EXAMPLE 576

4-[1-(4-*trans*-Cyclohexylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



To a solution of methyl 4-[4-(*trans*-4-cyclohexyl)cyclohexyl]aminomethyl]benzoate (338 mg, 1.03 mmol) in dichloromethane (8 mL) was added at room temperature 4-(trifluoromethoxy)-phenylisocyanate (210 mg, 1.03 mmol). After stirring for 16 hours at room temperature, the mixture was diluted with dichloromethane (10 mL), washed with 1N HCl (5 mL), brine (5 mL), dried (MgSO<sub>4</sub>), and concentrated. After flash chromatography (hexanes, ethyl acetate, 5:1), 487 mg of 4-[1-(4-*trans*-cyclohexylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-benzoic acid methyl ester was obtained.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.91 - 1.41 (m, 12H), 1.61 - 1.90 (m, 8H), 3.93 (s, 3H), 4.19 (m, 1H), 4.55 (s, 2H), 6.18 (s, 1H), 7.07 (d, 2H), 7.20 (d, 2H), 7.45 (d, 2H), 8.06 (d, 2H).

MS (APCI, pos.): 533.2 (M+1).

The above ester (487 mg, 0.99 mmol) was dissolved in THF (10 mL) and methanol (5 mL) and 1M KOH (4 mL) was added. The mixture was stirred at 80°C for 90 minutes, acidified with 1N HCl to pH = 4, and concentrated. The residue was dissolved in ethyl acetate (20 mL), washed with brine (10 mL), dried (MgSO<sub>4</sub>), and concentrated. The residue crystallized from hexane, ethyl acetate to afford 380 mg of 4-[1-(*trans*-4-cyclohexylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid white solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.91 - 1.15 (m, 10H), 1.37 (q, 2H), 1.63 (m, 8H), 4.04 (m, 1H), 4.60 (s, 2H), 7.21 (d, 2H), 7.34 (d, 2H), 7.53 (d, 2H), 7.86 (d, 2H), 8.54 (s, 1 H).

MS (APCI, pos.): 519.1 (M+1).

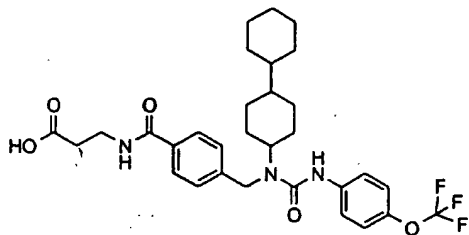
To a solution of above benzoic acid (380 mg, 0.71 mmol) in DMF (10 mL) was added diisopropylethylamine (0.38 mL, 275 mg, 2.12 mmol) and HBTU (320 mg, 0.86 mmol). After stirring for 15 minutes at room temperature, 5-aminotetrazole (150 mg, 1.45 mmol) was added. The mixture was stirred for 16 hours, and the solvent was evaporated. The residue was dissolved in ethyl acetate (20 mL), washed with water (2 x 10 mL), brine (10 mL), dried (MgSO<sub>4</sub>), and concentrated. The residue was dissolved in dichloromethane. On addition of ether, the title compound crystallized. Yield: 215 mg.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.82 - 1.18 (m, 10H), 1.40 (q, 2H), 1.63 (m, 8H), 4.03 (m, 1H), 4.63 (s, 2H), 7.21 (d, 2H), 7.41 (d, 2H), 7.57 (d, 2H), 8.03 (d, 2H), 8.56 (s, 1 H), 12.32 (s, 1H), 15.95 (s, 1H).

MS (APCI, pos.): 586.1 (M+1).

**EXAMPLE 577**

3-[4-[1-(4-Cyclohexylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino]-propionic acid



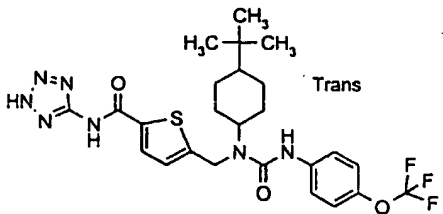
This compound was prepared similarly as described in examples 575 and 576 using the ethyl ester of 3-aminopropionate instead of 5-aminotetrazole followed by hydrolysis.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.07-0.08 (m, 2H), 1.05-1.13 (m, 5H), 1.32-1.50 (m, 6H), 1.64-1.91 (m, 7H), 2.51 (t, 2H), 3.48 (qt, 2H), 4.07 (brd m, 1H), 4.62 (s, 2H), 7.21 (d, 2H), 7.33 (d, 2H), 7.52 (d, 2H), 7.76 (d, 2H), 8.46 (brd t, 1H), 8.53 (brd s, 1H), 12.16 (brd s, 1H).

MS (APCI, pos): 590.3, 544.0, 518.2, 387.2, 388.2.

**EXAMPLE 578**

5-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]thiophene-2-carboxylic acid (2H-tetrazol-5-yl)amide



To a solution of methyl 5-formyl-thiophene-2-carboxylate (1.65 g, 9.6 mmol) (prepared according to C. Goddard, J. Heterocycl. Chem. 28, 1991, 17-28) in methanol (10 mL) was added 4-(*tert*-butylcyclohexyl)amine (*cis/trans* mixture). After standing at room temperature for 16 hours the precipitate was filtered off by suction to afford 1.82 g of 5-[(4-*trans*-*tert*-butylcyclohexylimino)methyl]thiophene-2-carboxylic acid methyl ester.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.87 (s, 9H), 1.07 - 1.17 (m, 3H), 1.51 - 1.63 (m, 2H), 1.77 - 1.88 (m, 4H), 3.13 (m, 1H), 3.88 (s, 3H), 7.25 (d, 1H), 7.72 (d, 1H), 8.36 (s, 1H).

The *trans*-imine from above (1.82 g, 5.9 mmol) was dissolved in dichloromethane (20 mL), and NaBH(OAc)<sub>3</sub> (1.5 g, 7.1 mmol) was added. The mixture was stirred for 16 hours at room temperature, diluted with water (20 mL), washed with NaHCO<sub>3</sub> solution (20 mL), brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. Flash chromatography (hexanes, ethyl acetate, 2:1) provided 692 mg of 5-[(4-*trans-tert*-butylcyclohexylamino)methyl]thiophene-2-carboxylic acid methyl ester.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.85 (s, 9H), 1.00 - 1.15 (m, 5H), 1.80 (m, 2H), 2.00 (m, 2H), 2.44 (m, 1H), 3.88 (s, 3H), 4.04 (s, 2H), 6.92 (d, 1H), 7.68 (d, 1H).

MS (APCI, pos.): 310.1 (M+1).

The above amine (692 mg, 2.23 mmol) was dissolved in dichloromethane (12 mL), and 4-trifluoromethoxyphenylisocyanate (454 mg, 2.23 mmol) was added. After stirring for 16 hours at room temperature, the mixture was concentrated. Flash chromatography (hexanes, ethyl acetate, 5:1) provided 1.1 g of 5-[1-(4-*trans-tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]thiophene-2-carboxylic acid methyl ester.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.87 (s, 9H), 0.98 (t, 1H), 1.12 - 1.27 (m, 2H), 1.48 (q, 2H), 1.88 (m, 4H), 3.89 (s, 3H), 4.04 (s, 2H), 3.98 (m, 1H), 4.65 (s, 2H), 6.42 (s, 1H), 7.06 (d, 1H), 7.13 (d, 2H), 7.37 (d, 2H), 7.71 (d, 1H). MS (APCI, pos.): 513.1 (M+1).

The above ester (1.1 g, 2.14 mmol) was dissolved in THF (15 mL) and methanol (2 mL) and 2M LiOH (5 mL) was added. The mixture was stirred at room temperature for 16 hours, acidified with 1N HCl to pH = 4, and concentrated. The residue was dissolved in ethyl acetate (20 mL), washed with brine (10 mL), dried (MgSO<sub>4</sub>), and concentrated. The residue crystallized from hexane, ethyl acetate to afford 745 mg of 5-[1-(4-*trans-tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]thiophene-2-carboxylic acid as a white solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.85 (s, 9H), 0.90 (q, 1H), 1.09 (q, 2H), 1.53 (q, 2H), 1.68 (m, 4H), 4.02 (m, 1H), 4.68 (s, 2H), 7.07 (d, 1H), 7.25 (d, 2H), 7.54 (d, 1H), 7.56 (d, 2H), 8.63 (s, 1H).

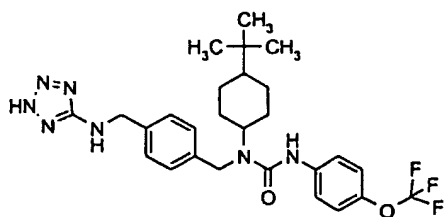
To a solution of above carboxylic acid (400 mg, 0.90 mmol) in DMF (7 mL) was added diisopropylethylamine (0.28 mL, 206 mg, 1.60 mmol) and HBTU (360 mg, 0.96 mmol). After stirring for 15 minutes at room temperature, 5-aminotetrazole (136 mg, 1.60 mmol) was added. After stirring for 72 hours, the solvent was evaporated. The residue was dissolved in ethyl acetate (20 mL), washed with water (2 x 10 mL), brine (10 mL), dried (MgSO<sub>4</sub>), and concentrated. Flash chromatography (hexanes, ethyl acetate, 1:2) afforded 120 mg of the title compound.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.83 (s, 9H), 0.96 (q, 1H), 1.12 (q, 2H), 1.50 (q, 2H), 1.73 (m, 4H), 3.96 (m, 1H), 4.70 (s, 2H), 7.14 (d, 1H), 7.24 (d, 2H), 7.55 (d, 2H), 8.04 (d, 1H), 8.64 (s, 1H), 12.37 (s, 1H), 15.92 (s, 1H).

MS (APCI, pos.): 566.1 (M+1).

#### 15 EXAMPLE 579

1-(4-*tert*-Butylcyclohexyl)-1-[4-[(2*H*-tetrazol-5-ylamino)methyl]benzyl]-3-(4-trifluoromethoxyphenyl)urea



To a suspension of 5-aminotetrazole (4.25g, 50 mmol) in ethanol (25 mL) was added triethylamine (6.9 mL, 5.05 g, 50 mmol). To the clear solution was added terephthalaldehyde mono (diethyl acetal) (10.4 g, 50 mmol). After stirring for 2 hours at room temperature, platinum oxide (150 mg) was added, and the mixture was hydrogenated at 50 psi for 16 hours. The catalyst was filtered off, and the filtrate was concentrated. On addition of water and conc. HCl, the residue crystallized. The solid was filtered off to give 4-[(2*H*-tetrazol-5-ylamino)methyl]benzaldehyde hydrochloride.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 4.50 (d, 2H), 7.33 (s, 1H), 7.54 (d, 2H), 7.66 (t, 1H), 7.88 (d, 2H), 9.98 (s, 1H).

30

MS (APCI, pos.): 204.0 (M+1).

To as suspension of above 4-[(2*H*-tetrazol-5-ylamino)methyl]benzaldehyde hydrochloride (1.0 g, 4.17 mmol) in methanol (10 mL) was added triethylamine, until a clear solution was obtained. 4-(*tert*-butylcyclohexyl)amine (*cis/trans*-mixture) (650 mg, 4.17 mmol) was added.

- 5 Acetic acid was added to adjust the pH to 6. The mixture was stirred at room temperature for 16 hours, and NaBH(OAc)<sub>3</sub> (1.0 g, 4.7 mmol) was added. After stirring for 16 hours at room temperature, the mixture was filtered and concentrated. The crude {4-[(4-*tert*-butylcyclohexyl-amino)methyl]benzyl}-(2*H*-tetrazol-5-yl)amine was used without further purification in the next step.

10

MS (APCI, pos.): 343.2 (M+1).

To a solution of above amine (288 mg, 0.84 mmol) in dichloromethane (10 mL) was added 4-trifluoromethoxyphenylisocyanate (180 mg, 0.84 mmol). After stirring for 16 hours at room  
15 temperature, the title compound (75 mg) crystallized out as a mixture of *cis* and *trans*-isomers.

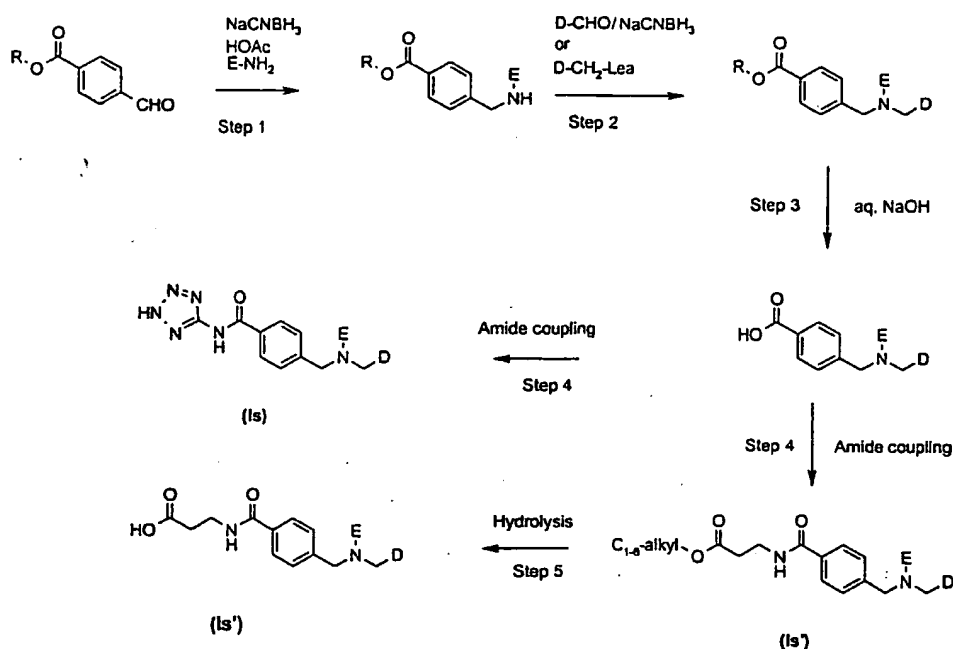
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<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.80, 0.82 (2 s, 9H), 0.92 (m, 1H), 1.09 (q, 2H), 1.34 - 1.51 (m, 3H), 1.64 - 1.75 (m, 3H), 4.00 (m, 0.75H), 4.21 (m, 0.25H), 4.35 (d, 2H), 4.53 (s, 1.5H), 4.64 (s, 0.5H), 7.14 (d, 1H), 7.16 - 7.29 (m, 6H), 7.53 (d, 2H), 7.55 (s, 1H), 8.46 (s, 0.75H), 8.55 (s, 0.25H).

MS (APCI, pos.): 546.2 (M+1).



General procedure (W) for the solution phase synthesis of compounds of general formulae (Is) and (Is'):



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wherein R is C<sub>1-6</sub>-alkyl,

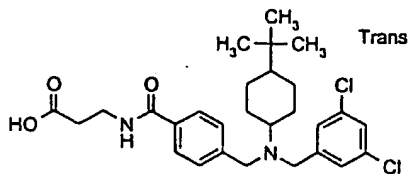
D and E are as defined in general formula (I) and

10 Lea is a leaving group such as chloro, bromo, iodo, mesyl or tosyl,

The general procedure (W) is illustrated by the following example.

EXAMPLE 580 (general procedure (W))

15 3-(4-[(*trans*-4-*tert*-Butylcyclohexyl)-(3,5-dichlorobenzyl)amino]methyl)benzoylamino)-propionic acid



Step 1: This step is identical to that described in general procedure (K), step 1.

Step 2: To a solution of the product obtained from step 1 (1.15 g, 3.8 mmol) and 3,5-dichloro-benzylchloride (0.74 g, 3.8 mmol) in acetonitrile (50 mL) was added potassium carbonate (0.79 g 5.7 mmol). The mixture was refluxed overnight. After cooling to room temperature, water (100 mL) was added, and the mixture was extracted with diethyl ether. The organic extract was dried (MgSO<sub>4</sub>) and concentrated to give crude product, which was purified by column chromatography to afford 1.7 g (97%) of 4-[[[(4-*tert*-butylcyclohexyl)-(3,5-dichloro-benzyl)amino]methyl]benzoic acid methyl ester.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.85(s, 9H), 1.22-1.59(m, 5H), 1.78-1.98(m, 4H), 2.41(m, 1H), 3.57(s, 2H), 3.66(s, 2H), 3.87(s, 3H), 7.18(s, 1H), 7.24(s, 2H), 7.40(d, 2H), 9.08(d, 2H).

LC-MS (APCI, pos.): 463(M+1).

Alternatively, step 2 can be performed as a reductive alkylation using an aldehyde (D-CHO instead of D-CH<sub>2</sub>-Lea) together with a reducing agent such as sodium cyanoborohydride.

Step 3: To a solution of the product from step 2 (1.7 g) in methanol (30 mL) was added 10% aqueous potassium hydroxide (10 mL) and the mixture was stirred at room temperature for 2 hours. The mixture was diluted with water and extracted with diethyl ether (2 × 30 mL). The aqueous layer was neutralised with dilute hydrochloric acid, and extracted with diethyl ether. The organic extract was dried (MgSO<sub>4</sub>) and concentrated to give 1.6 g (100%) of 4-[[[(4-*tert*-butylcyclohexyl)-(3,5-dichloro-benzyl)amino]methyl]benzoic acid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, δ): 8.01(s, 9H), 0.9-1.10(m, 4H), 1.66(m, 1H), 1.89(m, 2H), 2.32(m, 2H), 3.10(m, 1H), 4.21(s, 2H), 4.52(m, 2H), 7.58(s, 1H), 7.60-7.70(m, 3H), 7.88(d, 2H), 11.0(br, 1H).

LC-MS (APCI, pos.): 449 (M+1).

Step 4: To a solution of the product obtained in step 3 (1.6 g, 3.7 mmol) in DMF (30 mL) was added HBTU (1.5 g, 4.0 mmol) and diisopropylethylamine (1 g, 8 mmol). The mixture was stirred at 0°C for 30 minutes, and then β-alanine ethyl ester hydrochloride (1.2 g, 8 mmol) was added at 0°C. The reaction was monitored by TLC, and DMF was evaporated in vacuo

when the reaction was complete. The product from step 4 was used in the next step without further purification or characterisation.

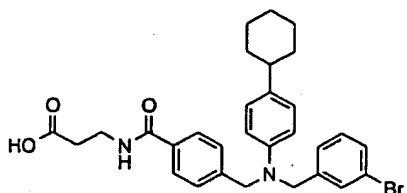
Step 5: To a solution of the product from step 4 (1.7 g) in methanol (30 mL) was added 2M aqueous lithium hydroxide (10 mL). The mixture was stirred at room temperature for 30 minutes and then diluted with water and washed with diethyl ether (2 × 30 mL). The aqueous layer was acidified with dilute hydrochloric acid and extracted with diethyl ether. The organic extract was dried (MgSO<sub>4</sub>) and concentrated to give a crude product, which was purified by HPLC to afford the title compound.

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>): δ 0.78 (s, 9H), 0.89 (m, 3H), 1.29 (qt, 2H), 1.77 (d, 2H), 1.85 (d, 2H), 2.31 (t, 1H), 2.47 (t, 2H), 3.42 (qt, 2H), 3.60 (s, 2H), 3.62 (s, 2H), 7.36 (m, 3H), 7.40 (d, 2H), 7.76 (d, 2H), 8.47 (t, 1H).

MS (APCI, pos): 519.2, 521.1

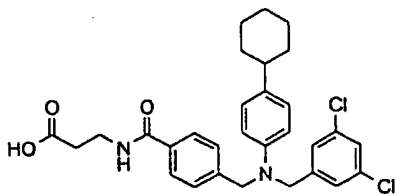
EXAMPLE 581 (General procedure (W))

3-(4-(((3-Bromobenzyl)-(4-cyclohexylphenyl)amino)methyl)benzoylamino)propionic acid



<sup>1</sup>H NMR: (MeOH-d<sub>4</sub>): δ 1.34–1.37 (m, 5H), 1.70–1.77 (m, 5H), 2.20 (m, 1H), 2.56 (t, 2H), 3.60 (t, 2H), 4.11 (s, 2H), 4.65 (s, 2H), 6.61 (d, 2H), 6.95 (d, 2H), 7.20 (d, 2H), 7.30 (m, 4H), 7.72 (d, 2H).

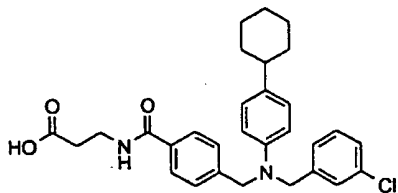
MS (APCI, pos): 551.1, 552.0

**EXAMPLE 582 (General procedure (W))****3-(4-(((4-Cyclohexylphenyl)-(3,5-dichlorobenzyl)amino)methyl)benzoylamino)propionic acid**

- 5 <sup>1</sup>H NMR: (DMSO-*d*<sub>6</sub>): δ 1.20-1.28 (m, 5H), 1.67-1.71 (m, 5H), 2.30 (m, 1H), 2.46 (t, 2H), 3.44 (qt, 2H), 4.69 (s, 2H), 4.73 (s, 2H), 6.53 (d, 2H), 6.94 (d, 2H), 7.28 (s, 2H), 7.31 (d, 2H), 7.47 (s, 1H), 7.77 (d, 2H), 8.49 (brd t, 1H).

MS (APCI, pos): 539.2, 541.0, 542.0

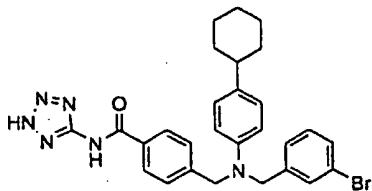
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**EXAMPLE 583 (General procedure (W))****3-(4-(((3-Chlorobenzyl)-(4-cyclohexylphenyl)amino)methyl)benzoylamino)propionic acid**

- 15 <sup>1</sup>H NMR: (DMSO-*d*<sub>6</sub>): δ 1.05-1.38 (m, 5H), 1.57-1.80(m, 5H), 2.29 (br, 1H), 2.46 (t, 2H), 3.42 (q, 2H), 4.68 (d, 4H), 6.53(d, 2H), 6.92 (d, 2H), 7.18-7.45 (m, 5H), 7.76(d, 2H), 8.46 (t, 1H), 12.3 (br, 1H).

LC-MS (APCI, pos.): 505 (M+1).

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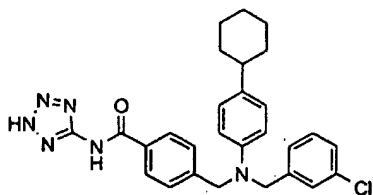
**EXAMPLE 584 (General procedure (W))****4-(((3-Bromobenzyl)-(4-cyclohexylphenyl)amino)methyl)-N-(2H-tetrazol-5-yl)benzamide**

<sup>1</sup>H NMR: (DMSO-*d*<sub>6</sub>): δ 1.16-1.27 (m, 5H), 1.69-1.72 (m, 5H), 2.29 (brd m, 1H), 4.71 (s, 2H), 4.77 (s, 2H), 6.54 (d, 2H), 6.94 (d, 2H), 7.28 (s, 2H), 7.42 (m, 4H), 8.03 (d, 2H), 12.25 (brd s, 1H), 16.00 (brd s, 1H).

5 MS (APCI, pos): 545.2

EXAMPLE 585 (General procedure (W))

4-[[[(3-Chlorobenzyl)-(4-cyclohexylphenyl)amino]methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



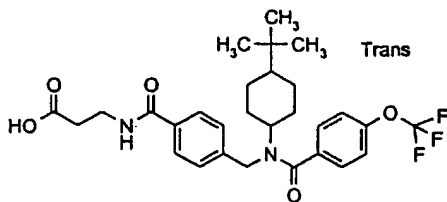
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<sup>1</sup>H NMR: (DMSO-*d*<sub>6</sub>): δ 1.16-1.24 (m, 5H), 1.60-1.70 (m, 5H), 2.30 (m, 1H), 4.71 (s, 2H), 4.77 (d, 2H), 6.54 (d, 2H), 6.93 (d, 2H), 7.21 (d, 1H), 7.29 (m, 2H), 7.34 (d, 1H), 7.41 (d, 2H), 8.05 (d, 2H), 12.36 (s, 1H), 16.04 (brd s, 1H).

15 MS (APCI, pos): 501.2, 503.1

EXAMPLE 586

3-(4-[[[(*trans*-4-*tert*-Butylcyclohexyl)-(4-trifluoromethoxybenzoyl)amino]methyl]benzoylamino)-propionic acid



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This compound was made from 3-{4-[[(*trans*-4-*tert*-butylcyclohexylamino)methyl]benzoylamino}propionic acid methyl ester with trifluoromethoxybenzoyl chloride according to a typical acylation procedure, followed by hydrolysis.

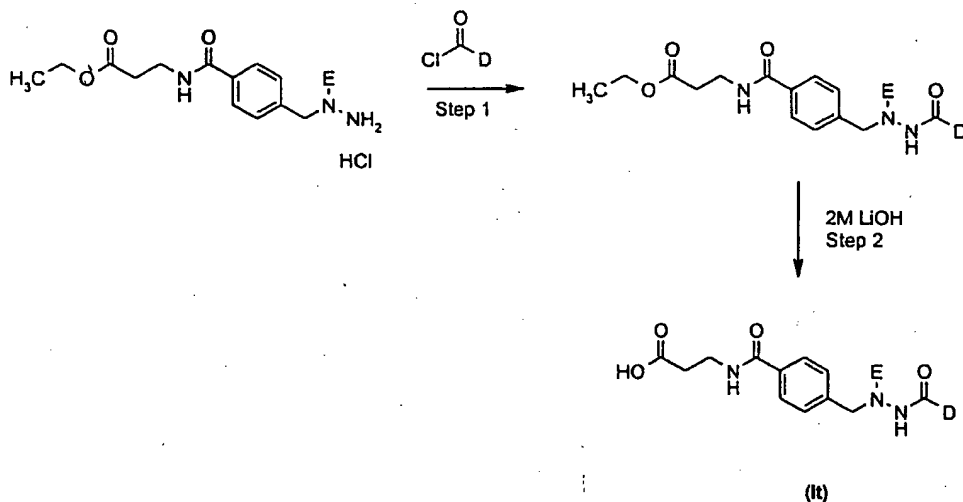
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<sup>1</sup>H NMR: (CDCl<sub>3</sub>): δ 0.76 (m, 10H), 1.46 (d, 2H), 1.60-1.80 (brd m, 6H), 2.60 (t, 2H), 3.56 (m, 1H), 3.63 (qt, 2H), 4.69 (s, 2H), 7.18 (m, 2H), 7.32 (m, 2H), 7.45 (m, 2H), 7.70 (d, 2H).

MS (APCI, pos): 549.2, 550.2

General procedure (X) for solution phase synthesis of compounds of the general formula (It):

5



wherein D and E are as defined for formula (I).

- 10 Step 1: Solutions of the desired acid chloride (0.01 mmol) in dichloroethane are placed into the appropriate wells of a 1 mL deep-well plate. A solution of the hydrazide (0.01 mmol) in dichloroethane, and a solution of triethylamine (0.05 mmol) in dichloroethane are then added into all of the wells of the deep-well plate. The reaction mixtures are allowed to react for 12 hours.

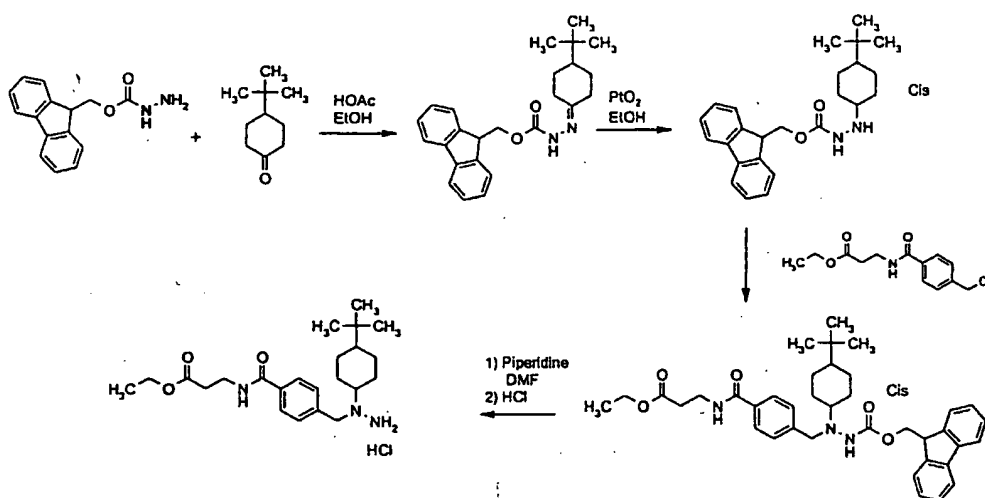
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Step 2: To the wells above are added excess aqueous 2M LiOH. After stirring the plates for at least three hours, the solvents are removed to afford the crude products.

The starting materials (hydrazines) can be prepared as follows:

Preparation of 3-{4-[*N*-(4-*cis*-*tert*-butylcyclohexyl)hydrazinomethyl]benzoylamino}propionic acid ethyl ester hydrochloride:

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Fmoc-hydrazide (12 g, 47.2 mmol) was dissolved in ethanol (400 mL) and 4-*tert*-butylcyclohexanone (8.73 g, 56.6 mmol) was added. Glacial acetic acid (4 mL) was added and the solution stirred for 18 hours at room temperature. The solution was concentrated to 1/4 its original volume and diluted with ethyl acetate (600 mL). The organic layer was washed with sat. aq NaHCO<sub>3</sub> (1 x 200 mL), brine (2 x 200 mL), dried over MgSO<sub>4</sub> and concentrated to give a yellow foam. Purification by silica gel flash chromatography eluting with 20% ethyl acetate/hexane to give *N'*-(4-*tert*-butylcyclohexylidene)hydrazinecarboxylic acid 9*H*-fluoren-9-ylethyl ester as a beige foam (16.9 g, 92% yield).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.98 (s, 1H), 7.89 (d, 2H), 7.48 (d, 2H), 7.43 (m, 2H), 7.31 (m, 2H), 4.29 (d, 2H), 2.12 (m, 1H), 1.80 (m, 4H), 1.12 (m, 4H), 0.86 (m, 10H).

APCI [M]<sup>+</sup> = 391.2.

The above cyclohexylidene compound (16.9 g, 43.3 mmol) was dissolved in anhydrous ethanol (400 mL) and PtO<sub>2</sub> (200 mg, 0.9 mmol) was added. The solution was stirred under a H<sub>2</sub> atmosphere (1 atm) at room temperature for 18 hours. The solution was passed through a bed of silica gel followed by two volumes of ethyl acetate and concentrated to give a yellow

foam. Purification by silica gel flash chromatography eluting with 10% ethyl acetate/hexane afforded *N'*-(4-*cis-tert*-butylcyclohexyl)hydrazinecarboxylic acid 9*H*-fluoren-9-ylmethyl ester as a white foam (12 g, 71% yield). By eluting with 15% ethyl acetate/hexane the corresponding *trans* isomer, *N'*-(4-*trans-tert*-butylcyclohexyl)hydrazinecarboxylic acid 9*H*-fluoren-9-ylmethyl ester, is obtained (2 g, 12% yield) as a white foam.

*cis* isomer: <sup>1</sup>H NMR (300 MHz) (CDCl<sub>3</sub>): δ 7.78 (d, 2H), 7.59 (d, 2H), 7.43 (m, 2H), 7.34 (m, 2H), 4.48 (d, 2H), 4.25 (t, 1H), 3.21 (m, 1H), 1.80 (m, 2H), 1.36 (m, 6H), 1.01 (m, 1H), 0.87 (s, 9H).

APCI [M]<sup>+</sup> = 393.2.

The above *cis* isomer (8 g, 20 mmol) was dissolved in acetonitrile (200 mL) and the 3-(4-chloromethylbenzoylamino)propionic acid ethyl ester (6 g, 22.4 mmol), potassium carbonate (8.4 g, 61 mmol), and sodium iodide (catalytic) were added and the solution was stirred at 50°C for 36 hours. The solution was diluted with ethyl acetate (800 mL) and washed with aqueous sat NaHCO<sub>3</sub> (3 x 300 mL), brine (3 x 300 mL), dried over MgSO<sub>4</sub> and concentrated to give a golden foam. Purification by silica gel flash chromatography eluting with 50% ethyl acetate/hexane afforded 3-{4-[*N*-(4-*cis-tert*-butylcyclohexyl)-*N'*-(9*H*-fluoren-9-ylmethyl-methoxycarbonyl)hydrazinomethyl]benzoylamino}propionic acid ethyl ester as a white foam (6 g, 47% yield).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.52 (t, 1H), 8.36 (s, 1H), 7.84 (d, 2H), 7.53 (d, 2H), 7.51 (t, 2H), 7.42 (m, 4H), 7.25 (t, 2H), 4.17 (d, 2H), 4.04 (m, 4H), 3.48 (m, 2H), 3.13 (m, 1H), 2.57 (d, 2H), 1.92 (m, 2H), 1.78 (m, 2H), 1.33 (m, 4H), 1.01 (m, 1H), 0.85 (s, 9H).

APCI [M]<sup>+</sup> = 626.3.

The above propionic acid ethyl ester (6 g, 9.6 mmol) was dissolved in DMF (15 mL) and piperidine (1.5 mL) was added while stirring at room temperature. TLC showed complete conversion after 10 minutes. The solution was diluted with ethyl acetate (350 mL) and washed with water (2 x 100 mL), brine (1 x 100 mL) and the organic layer was loaded directly onto a silica gel column packed with 20% ethyl acetate/hexane. 1 L of 20% ethyl acetate/hexane was flushed through the column followed by 50% ethyl acetate/hexane, followed by 80% ethyl acetate/hexane which eluded the product. To each 50 mL fraction that contained



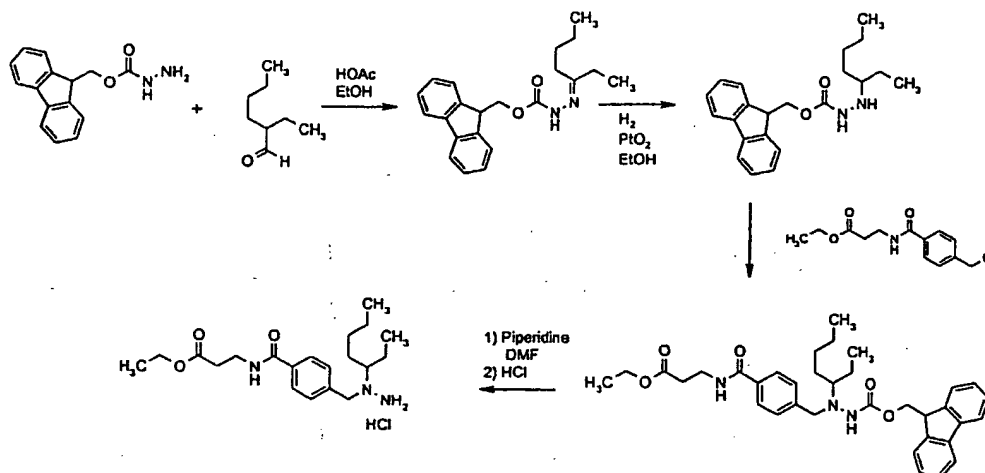
product, 4 mL of 1 M HCl/diethyl ether was added. The fractions were combined and concentrated to give 3-{4-[*N*-4-*cis-tert*-butylcyclohexyl]hydrazinomethyl]benzoylamino}propionic acid ethyl ester hydrochloride as an orange solid (3.6 g, 85.5% yield). The compound was used immediately in the next step.

5

APCI  $[M]^+ = 404.3$ .

Preparation of 3-{4-[*N*-(1-ethylpentyl)hydrazinomethyl]benzoylamino}propionic acid ethyl ester hydrochloride:

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Fmoc-hydrazide (12 g, 47.2 mmol) was dissolved in ethanol (400 mL) and 2-ethylhexanal (7.3 g, 56.6 mmol) was added. Glacial acetic acid (4 mL) was added and the solution stirred for 18 h at room temperature. *N*'-(1-ethylpentylidene)hydrazinecarboxylic acid 9*H*-fluoren-9-ylmethyl ester precipitated out of solution, and was collected by vacuum filtration and rinsed with ethanol to give beige needles (8 g, 47% yield).

APCI  $[M]^+ = 365.2$ .

20

The above ethylpentylidene compound (8 g, 21.9 mmol) was dissolved in anhydrous ethanol (600 mL) and  $\text{PtO}_2$  (150 mg, 0.68 mmol) was added. The solution was stirred under a  $\text{H}_2$  atmosphere (1 atm) at room temperature for 6 hours. The solution was passed through a bed of silica gel followed by two volumes of ethyl acetate and concentrated to give a white foam.

Purification by silica gel flash chromatography. eluting with 15% ethyl acetate/hexane af-

25

forded *N'*-(1-ethylpentyl)hydrazinecarboxylic acid 9*H*-fluoren-9-ylmethyl ester as a white foam (7 g, 87% yield): APCI  $[M]^+ = 367.2$ .

The above ethylpentyl compound (7 g, 19.1 mmol) was dissolved in acetonitrile (200 mL) and the 3-(4-chloromethylbenzoylamino)propionic acid ethyl ester (5.7 g, 21 mmol) was added. Potassium carbonate (7.9 g, 57.3 mmol) and sodium iodide (catalytic) were added and the solution was stirred at 50°C for 36 hours. The solution was diluted with ethyl acetate (800 mL) and washed with aqueous sat  $\text{NaHCO}_3$  (3 x 300 mL), brine (3 x 300 mL), dried over  $\text{MgSO}_4$  and concentrated to give a beige foam. Purification by silica gel flash chromatography eluting with 60% ethyl acetate/hexane to give 3-{4-[*N'*-(1-ethylpentyl)-*N'*-(9*H*-fluoren-9-ylmethylmethoxycarbonyl)hydrazinomethyl]benzoylamino}propionic acid ethyl ester as a white foam (6 g, 52.4% yield).

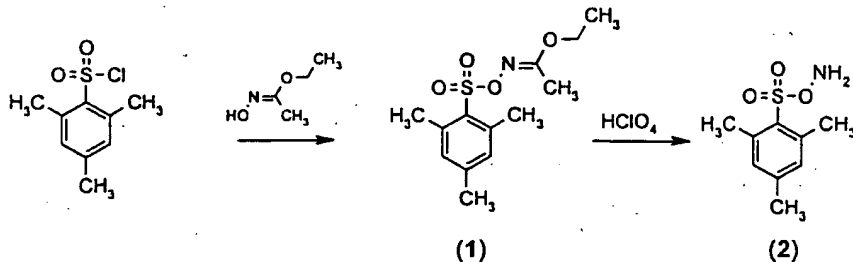
$^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.51 (t, 1H), 9.39 (s, 1H), 7.87 (d, 2H), 7.71 (d, 2H), 7.58 (d, 2H), 7.39 (m, 4H), 7.28 (m, 2H), 4.28 (m, 2H), 4.19 (d, 2H), 4.05 (q, 2H), 3.89 (s, 2H), 3.48 (q, 2H), 2.56 (m, 3H), 1.19 (m, 12H), 0.80 (m, 6H).

APCI  $[M]^+ = 600.3$ .

The above propionic acid ethyl ester compound (2.5 g, 4.2 mmol) was dissolved in DMF (15 mL) and piperidine (1.5 mL) was added while stirring at room temperature. TLC showed complete deprotection after 10 minutes. The solution was diluted with ethyl acetate (350 mL) and washed with  $\text{H}_2\text{O}$  (2 x 100 mL), brine (1 x 100 mL) and the organic layer was loaded directly onto a silica gel column packed with 20% ethyl acetate/hexane. 1 L of 20% ethyl acetate/hexane was flushed through the column followed by 50% ethyl acetate/hexane, followed by 80% ethyl acetate/hexane, which eluded the product. To each 50 mL fraction, which contained product, 4 mL of 1 M HCl/diethyl ether was added. The fractions were combined and concentrated to give 3-{4-[*N'*-(1-ethylpentyl)hydrazinomethyl]benzoylamino}propionic acid ethyl ester hydrochloride as an orange solid (1.2 g, 69.6% yield). The compound was used immediately in the next step.

APCI  $[M]^+ = 378.2$ .

451



Preparation of (1): See Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1.

- 5 Mesitylenesulfonyl chloride (6.75 g, 31 mmol) was added to a solution of ethyl acetohydroxamate (3.2 g, 31 mmol) and triethylamine (4.6 mL) in DMF (25 mL) dropwise over a period of 20 minutes while stirring on an ice bath. Stirring was continued for an additional 20 min at 0 – 10°C and the reaction mixture was poured into ice/water (100 mL). The solution was stirred for 10 min and a white solid precipitated. The product was collected by vacuum filtration and washed with water (200 mL). The solid was dissolved in diethyl ether (200 mL) and dried over  $\text{MgSO}_4$ . The solution was concentrated to give an off white solid which was dissolved in hot hexane. White crystals formed by placing the solution in a -30°C freezer overnight. The crystals were collected by filtration and dried with suction for one hour affording the product, (1) (6g, 90% yield).

15

$^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.71 (s, 2H), 3.84 (q, 2H), 2.56 (s, 6H), 2.29 (s, 3H), 2.01 (s, 3H), 1.12 (t, 3H).

APCI  $[\text{M}]^+ = 286.1$ .

20

Preparation of (2): See Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1.

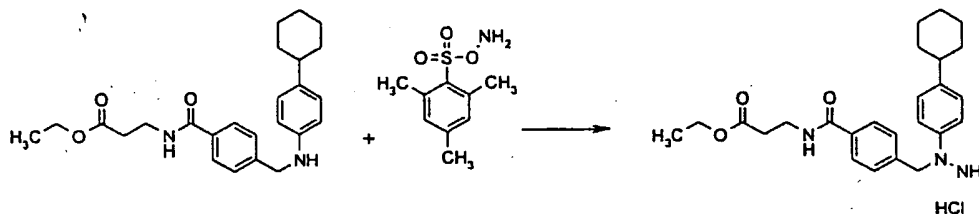
- To a solution of (1) (2 g, 6.7 mmol) in dioxane (8 mL) was added 70% perchloric acid (1.2 mL) dropwise while stirring at 0°C over a period of 10 minutes. The solution stirred for an additional 10 minutes at 0 – 10°C and the reaction mixture was poured into ice/water (100 mL). The solution was stirred for 10 min and a white solid precipitated. The solid was collected by filtration, washed with cold water (200 mL) followed by cold hexane (100 mL) and dried by maintaining suction for 1 hour to give the product, (2), as a white powder (1.4 g, 97% yield).

30

$^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.24 (bs, 2H), 6.78 (s, 2H), 2.51 (s, 6H), 2.18 (s, 3H).

APCI  $[M - NH_2]^+ = 199.0$ .

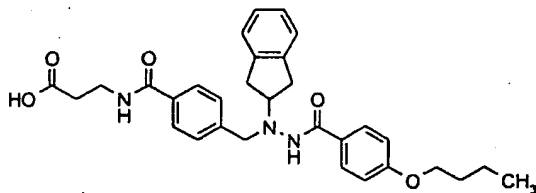
Preparation of 3-{4-[N-(4-cyclohexylphenyl)hydrazinomethyl]benzoylamino}propionic acid  
 5 ethyl ester hydrochloride:



3-{4-[(4-Cyclohexylphenylamino)methyl]benzoylamino}propionic acid ethyl ester (0.6 g, 1.47  
 10 mmol) was dissolved in dichloromethane (12 mL) and O-mesitylenesulfonylhydroxylamine  
 (0.79 g, 3.68 mmol) was added while stirring at 0°C. The solution stirred for 20 min. The solu-  
 tion was concentrated to 1/4 its original volume and loaded onto a silica gel column packed  
 with 25% ethyl acetate/hexane. The product was eluted with 5% methanol/ethyl acetate. To  
 each 50 mL fraction, which contained product, 4 mL of 1 M HCl/diethyl ether was added. The  
 15 fractions were combined and concentrated to give a rust colored solid. The solid was dis-  
 solved in ethyl acetate (10 mL) and hexane (20 mL) was added. A white precipitate formed  
 and was collected by filtration followed by rinsing with ethyl acetate to give 3-{4-[N-(4-cyclo-  
 hexylphenyl)hydrazinomethyl]benzoylamino}propionic acid ethyl ester hydrochloride as a  
 white solid (0.1 g, 15% yield). The product was stored in a freezer at -70°C until the next  
 20 step.

APCI  $[M]^+ = 424.2$ .

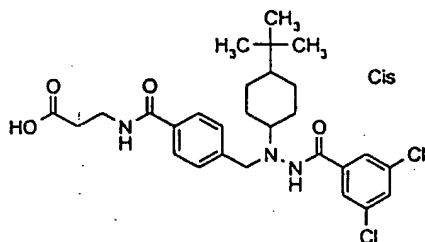
Examples of products prepared according to general procedure (X).

EXAMPLE 587 (General procedure (X))3-{4-[N'-(4-Butoxybenzoyl)-N-indan-2-yl]hydrazinomethyl}benzoylamino}propionic acid

- 5 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.91 (t, 3H), 1.41 (quintet, 2H), 1.67 (quintet, 2H), 2.49 (t, 2H, 3.96 (t, 2 H), 4.15 (m, 2 H), 6.88 (d, 2H), 7.09 - 7.18 (m, 2H), 7.10 - 7.20 (m, 2H), 7.50 (t, 4H), 7.72 (d, 2H), 8.47 (t, 1 H), 9.13 (s, 1 H).

MS (APCI, pos.): 530.2.

10

EXAMPLE 588 (General procedure (X))3-{4-[N-(*cis*-4-*tert*-Butylcyclohexyl)-N'-(3,5-dichlorobenzoyl)hydrazinomethyl]benzoylamino}-propionic acid

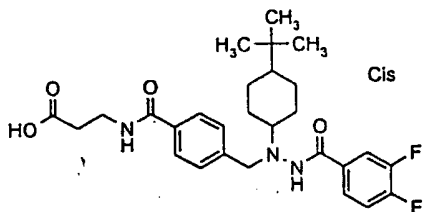
15

- <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.85 (s, 9H), 1.04 (m, 1H), 1.37 (m, 4H), 1.58 (m, 2H), 1.92 (m, 2H), 2.44 (t, 2H), 3.42 (t, 2H), 4.16 (m, 3H), 7.44 (d, 2H), 7.58 (s, 2H), 7.74 (d, 2 H), 7.75 (s, 1H), 8.48 (t, 1H), 9.42 (s, 1H).

- 20 MS (APCI, pos.): 548.2, 550.1.

EXAMPLE 589 (General procedure (X))

3-{4-[N-(cis-4-tert-Butylcyclohexyl)-N'-(3,4-difluorobenzoyl)hydrazinomethyl]benzoylamino}-propionic acid



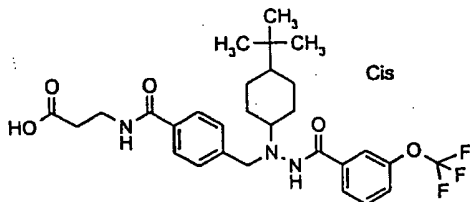
5

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.85 (s, 9H), 1.03 (m, 1H), 1.36 (m, 4H), 1.59 (m, 2H), 1.92 (m, 2H), 2.44 (t, 2H), 3.41 (t, 2H), 4.04 (m, 3H), 7.46 (m, 4H), 7.60 (q, 1H), 7.72 (d, 2H), 8.47 (t, 1H), 9.30 (s, 1H).

10 MS (APCI, pos.): 516.2.

EXAMPLE 590 (General procedure (X))

3-{4-[N-(cis-4-tert-Butylcyclohexyl)-N'-(3-trifluoromethoxybenzoyl)hydrazinomethyl]benzoylamino}propionic acid



15

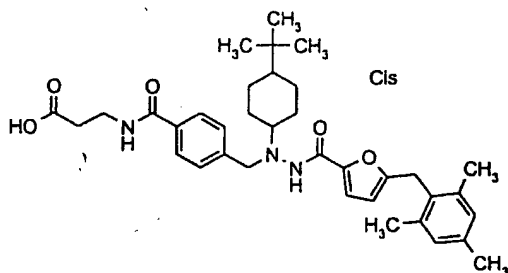
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.87 (s, 9H), 1.08 (m, 1H), 1.38 (m, 4H), 1.61 (m, 2H), 1.95 (m, 2H), 3.41 (t, 2H), 4.10 (m, 2H), 7.45 – 7.53 (m, 3H), 7.62 (d, 1H), 7.74 (d, 1H), 8.44 (t, 1H), 9.38 (s, 1H), 12.19 (s, 1H).

20

MS (APCI, pos.): 564.2.

EXAMPLE 591 (General procedure (X))

3-(4-(N-(*cis*-4-*tert*-Butylcyclohexyl)-N'-[5-(2,4,6-trimethylbenzyl)furan-2-carbonyl]hydrazino-methyl)benzoylamino)propionic acid



<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.86 (s, 9H), 1.10 (s, 1H), 1.25 – 1.35 (m, 4H), 1.57 (m, 2H), 1.91 (m, 2H), 2.20 (s, 9H), 2.47 (t, 2H), 3.31 (m, 1H), 3.42 (t, 2H), 3.90 (s, 2H), 4.08 (m, 2H), 7.79 (s, 1H), 6.83 (s, 2H), 6.85 (d, 1H), 7.47 (d, 1H), 7.73 (d, 1H), 8.48 (t, 1H), 8.90 (s, 1H), 12.18 (s, 1H).

Preparation of 5-(2,4,6-trimethylbenzyl)furan-2-carbonyl chloride:

Step A: 1,3,5-Trimethylbenzene (6.85 g, 57 mmol), methyl 5-chloromethyl-2-furanoate (2.48 g, 14.2 mmol) and aluminum trichloride (2.46 g, 18 mmol) were refluxed in dichloromethane (30 mL) for 4 h. The reaction was quenched with water, and the two layers were separated.

The organic layer was concentrated and passed through a silica gel column. Hexane was used as the mobile phase to elute the product. The 5-(2,4,6-trimethylbenzyl)furan-2-carboxylic acid methyl ester was obtained as a yellow oil (86%).

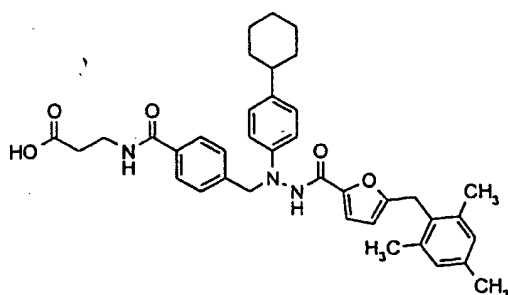
Step B: The methyl ester (2.9 g, 11.6 mmol) from above was dissolved in methanol (50 mL) and 4 M NaOH (12 mL, 46.5 mmol) was added. The reaction was stirred overnight and made acidic using 1 N HCl. The reaction mixture was concentrated, dissolved in ethyl acetate, washed with brine, and dried over MgSO<sub>4</sub>. Upon evaporation of the solvent, the corresponding carboxylic acid was obtained as a light yellow solid (2.7 g, 98%).

Step C: The furanyl carboxylic acid (2.59 g, 0.6 mmol) was dissolved in dichloromethane (20 mL) and thionyl chloride (10 mL, 106 mmol) was added dropwise. The reaction was refluxed for 3 hours and concentrated to dryness. The residue was passed through a silica gel plug-column using dichloromethane. The 5-(2,4,6-trimethylbenzyl)furan-2-carbonyl chloride was obtained as a yellow solid upon evaporation of the solvent (2.7 g, 97%).

MS (APCI, pos.): 602.3

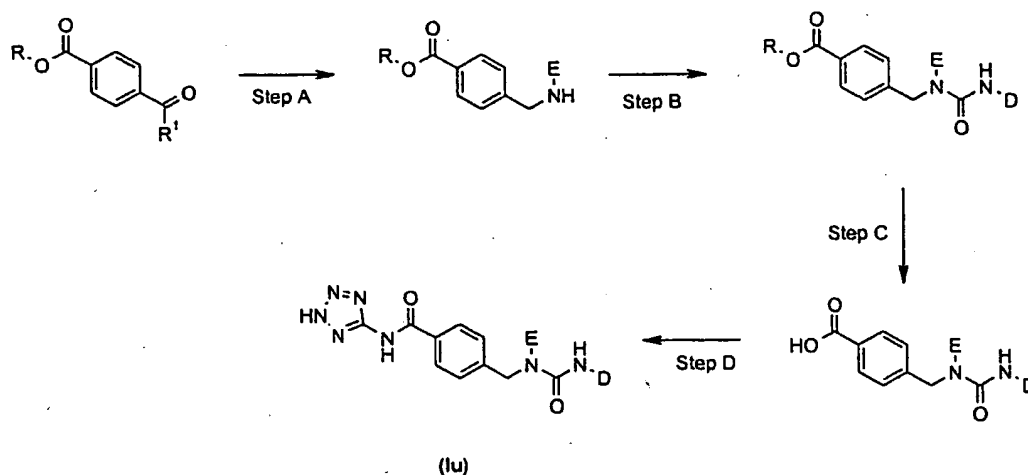
EXAMPLE 592 (General procedure (X))

3-(4-{N-(4-Cyclohexylphenyl)-N'-[5-(2,4,6-trimethylbenzyl)furan-2-carbonyl]hydrazinomethyl}-benzoylamino)propionic acid



$^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$  1.20-1.38 (m, 5H), 1.70-1.80 (m, 5H), 2.24 (s, 3H), 2.27 (s, 6H), 2.41 (m, 1H), 2.65 (t, 2H), 3.65 (qt, 2H), 3.94 (s, 2H), 4.84 (s, 2H), 5.92 (s, 1H), 6.81 (d, 2H), 6.85 (d, 2H), 7.04 (s, 1H), 7.06 (d, 2H), 7.58 (d, 2H), 7.84 (d, 2H), 9.61 (s, 1H).

MS (APCI, pos): 620.2, 621.3.

General procedure (Y) for solution phase preparation of compounds of general formula (Iu):

wherein

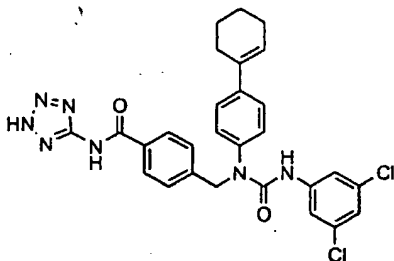
E and D are as defined for formula (I) and



R is C<sub>1-8</sub>-alkyl.

Example 593 (General procedure (Y))

- 5 4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide



4-Cyclohex-1-enylaniline:

- 10 A mixture of cyclohexanone (50 g, 0.325 mol), and aniline (95 g, 1 mol) in 12 M HCl (100 mL), and ethanol (15 mL) was refluxed at 110°C for four days. The solution was cooled and diluted with ethyl acetate. The aqueous layer was basified with 6 M NaOH. The organic layer was separate and washed with brine (3x), dried over MgSO<sub>4</sub>, and concentrated to give a brown oil. Approximately half of the crude product was introduced into a silica gel column  
15 and eluted with 5% ethyl acetate/hexane to obtain the desired product along with aniline. The combined organic fractions were extracted with 1 N HCl and separated. Addition of brine to the aqueous layer precipitated the 4-cyclohex-1-enylaniline as a cream colored solid (9 g).

- <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.50-1.60 (m, 2H), 1.60-1.70 (m, 2H), 2.10-2.15 (m, 2H), 2.20-2.30 (brd s, 2H), 5.00 (s, 2H), 5.90 (t, 1H), 6.50 (d, 2H), 7.10 (d, 2H).
- 20

- Step A: To a solution of E-NH<sub>2</sub> (eg 4-cyclohexenylaniline, prepared as described above) (0.023 mol) and methyl 4-formylbenzoate (3.77 g, 0.023 mol) in dichloromethane (50 mL) and methanol (15 mL) was added a catalytic amount of acetic acid. After stirring the solution  
25 for 3 hours, Na(OAc)<sub>3</sub>BH (24 g, 0.115 mol) was added. The reaction was allowed to stir at room temperature for 16 hours. The reaction mixture was diluted with ethyl acetate and washed with aqueous sodium bicarbonate (3x), brine (2x), dried over MgSO<sub>4</sub>, filtered, and concentrated to give an orange solid. The crude product was introduced into a column of silica gel and eluted with ethyl acetate/hexane (5/95) to give 4-[(4-cyclohex-1-enylphenyl-amino)methyl]benzoic acid methyl ester (5g, 0.015 mol).
- 30

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.56 (m, 2H), 1.67 (m, 2H), 2.11 (m, 2H), 2.25 (m, 2H), 3.81 (s, 3H), 4.34 (d, 2H), 5.89 (t, 1H), 6.34 (t, 1H), 6.49 (d, 2H), 7.10 (d, 2H), 7.47 (d, 2H), 7.90 (d, 2H).

5 MS (APCI, pos): 322.1, 323.1.

Step B: The above 4-[(4-cyclohex-1-enylphenylamino)methyl]benzoic acid methyl ester (5 g, 0.015 mol) was dissolved in anhydrous dichloromethane and diisopropylethylamine (5.8 g, 0.045 mol) was added. To this solution was added an isocyanate (eg. 3,5-dichlorophenyl-  
10 isocyanate) (0.018 mol). After stirring the reaction mixture for 3 hours, the solution was diluted with ethyl acetate and washed with 1N HCl (2x), water, brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was introduced into a silica gel column and eluted with ethyl acetate/hexane (10/90) to give 4-[3-(3,5-dichlorophenyl-1-(cyclohex-1-enylphenyl)ureidomethyl]benzoic acid methyl ester (4 g).

15

MS (APCI, pos): 509.0, 510.0, 511.1.

Step C: To a solution of the above 4-[3-(3,5-dichlorophenyl-1-(cyclohex-1-enylphenyl)ureidomethyl]benzoic acid methyl ester (1.5 g, 2 mmol) in THF (30 mL) and methanol (10 mL) was  
20 added an excess of 2 M LiOH (10 mL). After stirring the reaction mixture for 3 hours, the solution was concentrated. The residue was taken up in ethyl acetate and washed with 1 N HCl (2x), H<sub>2</sub>O (2x), brine, and dried over MgSO<sub>4</sub>. Evaporation of the solvent gave the product as an oil. The oil was taken up in dichloromethane. Upon sitting, 4-[3-(3,5-dichlorophenyl-1-(cyclohex-1-enylphenyl)ureidomethyl]benzoic acid (1.2 g, quantitative) crystallized out of so-  
25 lution.

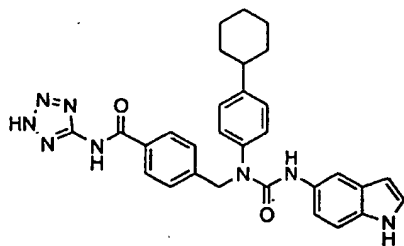
Step D: To a solution of the above benzoic acid (0.4 g, 0.81 mmol) in DMF (4 mL) was added HBTU (0.37 g, 0.90 mmol), diisopropylethylamine (0.30 g, 2.4 mmol), and 5-aminotetrazole (0.24 g, 2.4 mmol). After stirring the solution for 16 hours, the reaction mixture was diluted  
30 with ethyl acetate and washed with 1N HCl (3x), brine (3x), dried over MgSO<sub>4</sub>, filtered, and concentrated to a syrup. By addition of dichloromethane to the oil, the title compound precipitated as a creamy-white solid (200 mg, 0.36 mmol).

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.52-1.78 (m, 4H), 2.08-2.25 (br, 2H), 2.26-2.40 (br, 2H), 5.00 (s, 2H), 6.19 (br, 1H), 7.14 (s, 1H), 7.22 (d, 2H), 7.36-7.50 (dd, 4H), 7.62 (s, 2H), 8.03 (d, 2H), 12.37 (s, 1H), 16.02 (s, 1H).

5 LC-MS (APCI, pos.): 562 (M+1).

Example 594 (General procedure (Y))

4-[1-(4-Cyclohexylphenyl)-3-(1*H*-indol-5-yl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



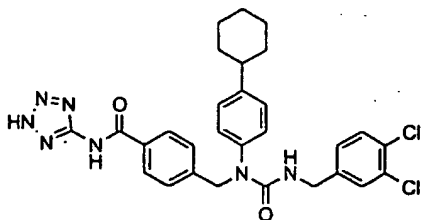
10

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.12-1.46 (m, 5H), 1.62-1.83 (m, 5H), 5.01 (s, 1H), 6.32 (s, 1H), 7.05-7.08 (q, 1H), 7.17-7.29 (m, 6H), 7.48 (d, 2H), 7.55 (s, 1H), 7.85 (s, 1H), 8.05 (d, 2H), 10.9 (s, 1H), 12.36 (s, 1H), 16.0-16.2 (br, 1H).

15 MS (APCI, pos.): 535 (M+1).

Example 595 (General procedure (Y))

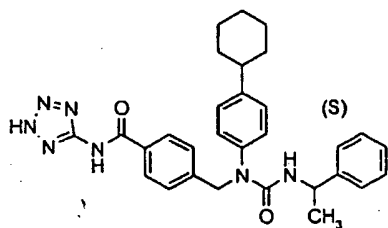
4-[1-(4-Cyclohexylphenyl)-3-(3,4-dichlorobenzyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



20

<sup>1</sup>H NMR: (DMSO-*d*<sub>6</sub>): δ 1.20 (m, 1H), 1.30-1.50 (m, 4H), 1.60-1.70 (m, 5H), 4.21 (s, 2H), 4.89 (s, 2H), 6.60 (m, 1H), 7.14 (d, 2H), 7.21 (d, 3H), 7.39 (d, 2H), 7.46 (s, 1H), 7.56 (d, 1H), 8.03 (d, 2H), 12.30 (s, 1H), 16.00 (brd s, 1H).

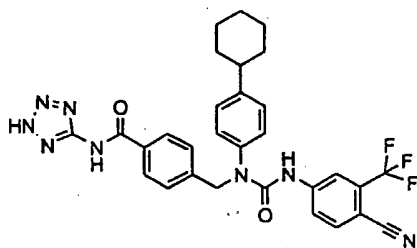
25 MS (APCI, pos): 578.1, 579.1, 580.1

Example 596 (General procedure (Y))4-[1-(4-Cyclohexylphenyl)-3-((1S)-1-phenylethyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

- 5  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.15-1.45 (m, 9H), 1.64-1.80 (m, 5H), 4.82-4.98 (m, 3H), 6.16 (d, 2H), 7.08-7.38 (m, 11H), 7.98 (d, 2H), 11.0 (br, 1H).

LC-MS (APCI, pos.): 524 (M+1).

10 Example 597 (General procedure (Y))

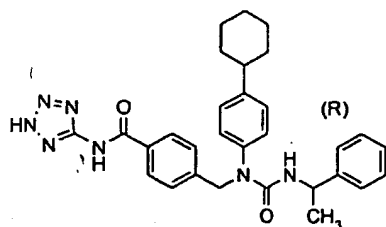
4-[1-(4-Cyclohexylphenyl)-3-(4-cyano-3-trifluoromethylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

- 15  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.10-1.90 (m, 10H), 2.30 (br, 1H), 5.02 (s, 2H), 7.18-7.40 (m, 4H), 7.45 (d, 2H), 7.95-8.20 (m, 5H), 9.14 (s, 1H), 12.34 (s, 1H).

LC-MS (APCI, pos.): 589 (M+1).

Example 598 (General procedure (Y))

4-[1-(4-Cyclohexylphenyl)-3-((1R)-1-phenylethyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide

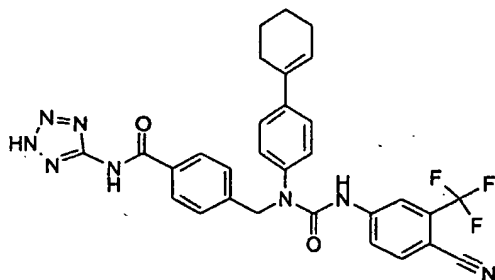


<sup>1</sup>H NMR (acetone-*d*<sub>6</sub>): δ 1.18-1.48 (m, 9H), 1.68-1.88 (m, 4H), 2.52 (m, 1H), 4.98 (s, 2H), 5.05 (m, 1H), 5.37 (d, 1H), 7.15-7.35 (m, 9H), 7.47 (d, 2H), 8.09 (d, 2H), 11.3 (br, 1H).

LC-MS (APCI, pos.): 524 (M+1).

EXAMPLE 599 (general procedure (Y))

4-[3-(4-Cyano-3-trifluoromethylphenyl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



HPLC-MS (method B): *m/z*: 587. *R*<sub>t</sub> = 7.65 min.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.55-1.63 (2H, m), 1.68-1.76 (2H, m), 2.17 (2H, broad), 2.35 (2H, broad), 5.05 (2H, s), 6.20 (1H, broad), 7.28 (2H, d), 7.43 (4H, dd), 8.02 (5H, m), 8.18 (1H, s), 9.20 (1H, s), 12.35 (1H, s).

Microanalysis: calculated for C<sub>30</sub>H<sub>25</sub>F<sub>3</sub>N<sub>8</sub>O<sub>2</sub>·0.5 mol H<sub>2</sub>O:

60.50% C; 4.40% H; 18.81% N; Found:

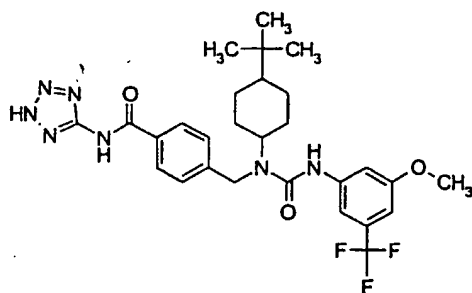
60.80% C; 4.49% H; 18.51% N.



54.25% C; 4.02% H; 15.16% N.

EXAMPLE 602 (general procedure (Y))

4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-methoxy-5-trifluoromethylphenyl)ureidomethyl]-*N*-(2H-tetrazol-5-yl)benzamide



HPLC-MS (method B):  $m/z$ : 574,  $R_t$  = 7.85 min.

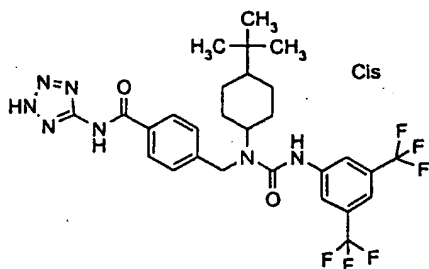
$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  0.83 (9H,s), 0.96 (1H,m), 1.14 (2H,m), 1.44 (2H,m), 1.73 (4H,m), 3.80 (3H, s), 4.08 (1H,m), 4.68 (2H,s), 6.82 (1H,s), 7.42 (2H,d), 7.46 (1H,s), 7.53 (1H,s), 8.05 (2H,d), 8.71 (1H,s), 12.36 (1H,s).

Microanalysis: calculated for  $\text{C}_{28}\text{H}_{34}\text{F}_3\text{N}_7\text{O}_3$ :

58.63% C; 5.97% H; 17.09% N; Found:  
58.45% C; 6.29% H; 17.04% N.

EXAMPLE 603 (general procedure (Y))

4-[3-(3,5-Bis(trifluoromethyl)phenyl)-1-(*cis*-4-*tert*-butylcyclohexyl)ureidomethyl]-*N*-(2H-tetrazol-5-yl)benzamide

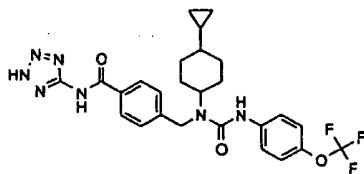


HPLC-MS (method B):  $m/z$ : 512,  $R_t$  = 8.20 min.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  0.83 (9H,s), 1.20 (1H,m), 1.35 (2H,m), 1.55 (4H,m), 1.77 (2H,m), 4.31 (1H,m), 4.76 (2H,s), 7.42 (2H,d), 7.61 (1H,s), 8.05 (2H,d), 8.26 (2H, s), 9.12 (1H, s), 12.32 (1H,s).

5 **EXAMPLE 604**

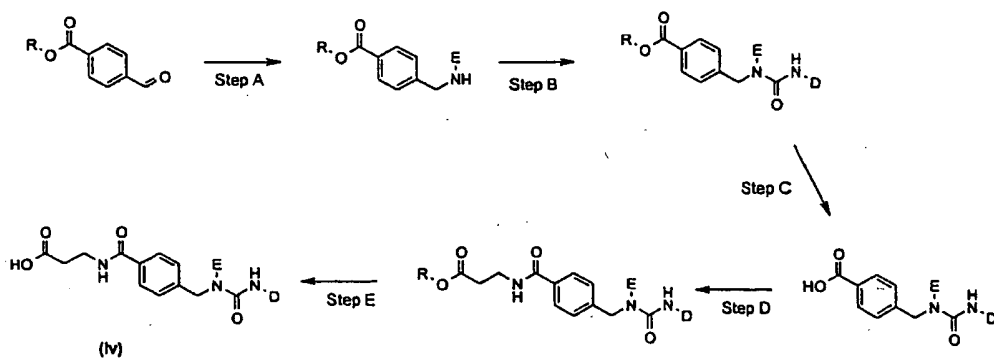
4-[1-(4-Cyclopropylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



10  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  12.2 (s, broad), 8.59 (1H, s), 8.03 (2H, d), 7.55 (2H, d), 7.42 (2H, d), 7.22 (2H, d), 4.63 (2H, broad), 4.12 (1H, m), 1.80-1.00 (9H, m), 0.49 (2H, m), 0.35 (2H, m).

HPLC-MS (method B):  $m/z$ : 544,  $R_t$  = 7.70 min.

15 General procedure (Z) for solution phase preparation of compounds of general formula (iv):



wherein

20

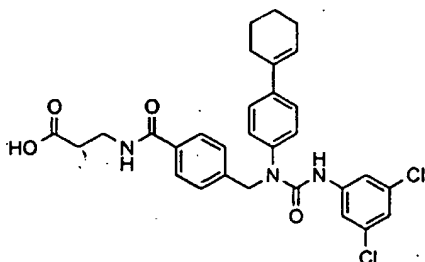
E and D are as defined for formula (I) and

R is  $\text{C}_{1-6}$ -alkyl.



Example 605 (General procedure (Z))

3-{4-[1-(4-Cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-propionic acid



5

Steps A to C of this general procedure (Z) are similar to steps A to C of the general procedure (Y).

Step D: To a solution of the above benzoic acid (0.4 g, 0.81 mmol, prepared in step C) in DMF (4 mL) were added HBTU (0.37 g, 0.90 mmol), diisopropylethylamine (0.30 g, 2.4 mmol), and ethyl 3-aminopropanoate hydrochloride (0.30 g, 2.4 mmol). After stirring the solution for 16 hours, the reaction was diluted with ethyl acetate and washed with 1N HCl (3x), brine (3x), dried over  $\text{MgSO}_4$ , filtered, and concentrated to a syrup. The crude material was introduced into a silica gel column and eluted with ethyl acetate/hexane (1/3 to 4/6) to afford 3-{4-[1-(4-cyclohex-1-enylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-propionic acid ethyl ester in quantitative yield.

Step E: The propionic acid ethyl ester prepared in step D was dissolved in THF (6 mL) and MeOH (3 mL). A solution of 2 M LiOH (3 mL) was then added and the reaction was stirred at room temperature for 30 minutes. The solvents were evaporated under reduced pressure. The residue was taken up in ethyl acetate and washed with 1 N HCl (2x), brine (2x), dried over  $\text{MgSO}_4$ , filtered, and concentrated to a syrup. Addition of hexane followed by trituration precipitated the title compound (270 mg, 0.48 mmol) as a cream colored solid.

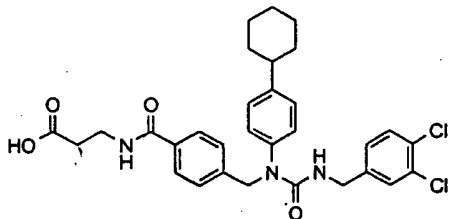
$^1\text{H}$  NMR (acetone- $d_6$ ):  $\delta$ : 1.58-1.85 (m, 4H), 2.15-2.28 (m, 2H), 2.32-2.44 (m, 2H), 2.65 (t, 2H), 3.63 (q, 2H), 5.01 (s, 2H), 6.24 (m, 1H), 7.04 (m, 1H), 7.22 (d, 2H), 7.38-7.48 (m, 4H), 7.61 (d, 2H), 7.70-7.88 (m, 4H), 10.7 (br, 1H).

LC-MS (APCI, pos.): 567(M+1).

30

Example 606 (General procedure (Z))

3-{4-[1-(4-Cyclohexylphenyl)-3-(3,4-dichlorobenzyl)ureidomethyl]benzoylamino}propionic acid



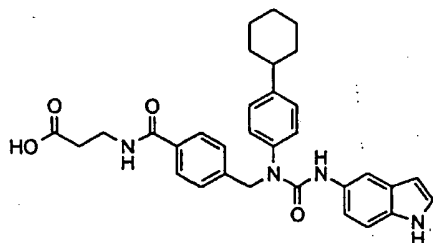
5

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.15 (m, 1H), 1.34 (t, 4H), 1.70 (m, 1H), 1.75 (d, 4H), 2.45 (t, 2H), 3.45 (qt, 2H), 4.20 (d, 2H), 4.84 (s, 2H), 6.56 (t, 1H), 7.08 (d, 2H), 7.19-7.27 (m, 5H), 7.45 (s, 1H), 7.57 (d, 1H), 7.73 (d, 2H), 8.48 (t, 1H), 12.21 (s, 1H).

10 MS (APCI, pos): 582.1, 583.1, 584.1

Example 607 (General procedure (Z))

3-{4-[1-(4-Cyclohexylphenyl)-3-(1H-indol-5-yl)ureidomethyl]benzoylamino}propionic acid



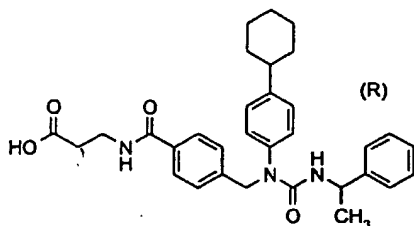
15

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$ : 1.12-1.45 (m, 5H), 1.63-1.87 (m, 5H), 2.40-2.55 (br, 2H), 3.43 (q, 2H), 4.96 (s, 2H), 6.32 (s, 1H), 7.0-7.08 (q, 1H), 7.13-7.29 (m, 6H), 7.36 (d, 2H), 7.54 (s, 1H), 7.76 (m, 3H), 8.48 (t, 1H), 10.9 (s, 1H).

20 LC-MS (APCI, pos.): 539 (M+1).

Example 608 (General procedure (Z))

3-{4-[1-(4-Cyclohexylphenyl)-3-((1R)-1-phenylethyl)ureidomethyl]benzoylamino}propionic acid



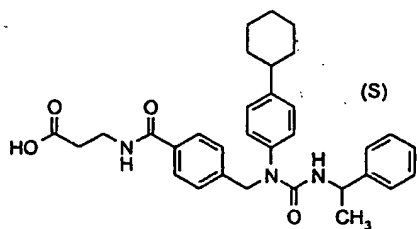
5

<sup>1</sup>H NMR (acetone-*d*<sub>6</sub>): δ 1.18-1.48 (m, 9H), 1.68-1.90 (m, 4), 2.51 (m, 1H), 2.65 (t, 2H), 3.63 (q, 2H), 4.91 (s, 2H), 5.03 (m, 1H), 5.28 (d, 1H), 7.08-7.35 (m, 11H), 7.70-7.82 (m, 3H), 10.7 (br, 1H).

10 LC-MS (APCI, pos.): 528 (M+1).

Example 609 (General procedure (Z))

3-{4-[1-(4-Cyclohexylphenyl)-3-((1S)-1-phenylethyl)ureidomethyl]benzoylamino}propionic acid



15

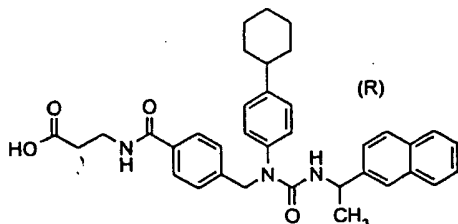
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.12-1.40 (m, 9H), 1.62-1.85 (m, 5H), 2.50 (t, 2H), 3.43 (q, 2H), 4.78-4.95 (m, 3H), 6.09 (d, 2H), 7.07 (d, 2H), 7.14-7.34 (m, 9H), 7.73 (d, 2H), 8.44 (s, 1H), 12.15 (s, 1H).

20

LC-MS: (APCI, pos.): 528 (M+1).

Example 610 (General procedure (Z))

3-[4-[1-(4-Cyclohexylphenyl)-3-[(1R)-1-(2-naphthyl)ethyl]ureidomethyl]benzoylamino]-  
propionic acid



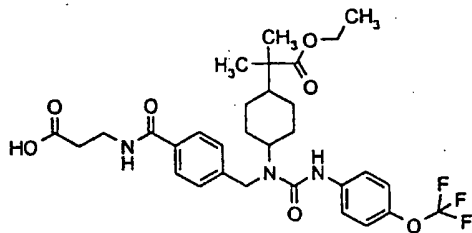
5

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.15-1.86 (m, 14H), 2.50 (t, 2H), 3.44 (q, 2H), 4.87 (s, 2H), 5.06 (t, 1H), 6.26 (d, 2H), 7.10 (d, 2H), 7.19 (d, 2H), 7.26 (d, 2H), 7.43-7.50 (m, 3H), 7.68-7.76 (m, 3H), 7.80-7.91 (m, 3H), 8.44 (s, 1H), 12.13 (s, 1H).

10 LC-MS (APCI, pos.): 578 (M+1).

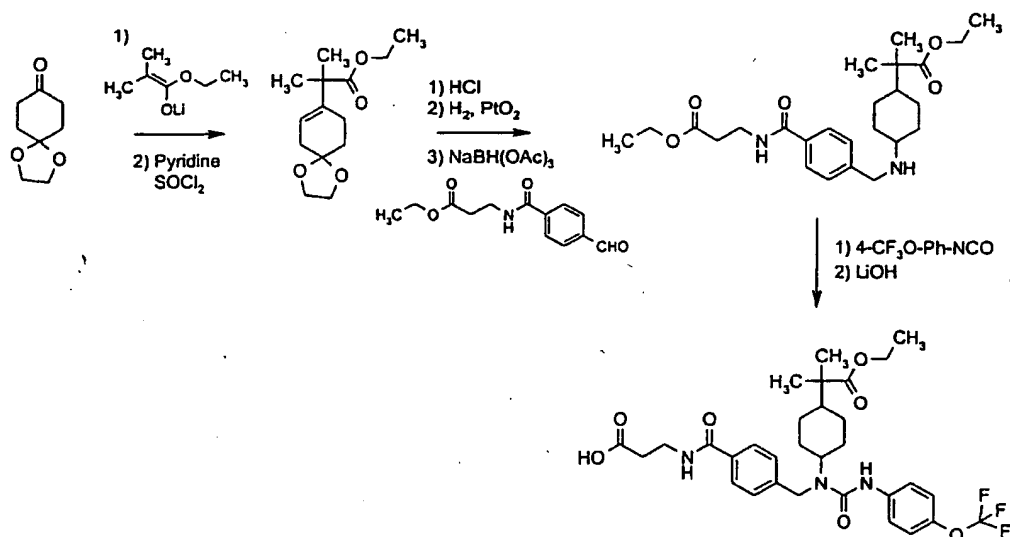
EXAMPLE 611

2-[4-[1-[4-(2-Carboxyethylcarbamoyl)benzyl]-3-(4-trifluoromethoxyphenyl)ureido]cyclohexyl]-  
2-methylpropionic acid ethyl ester



15

Reaction scheme:



Ethyl 2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-2-methylpropanoate:

5

To a solution of diisopropylamine (10.1g, 0.1mol) in THF (50 mL) at  $-78^{\circ}\text{C}$  was added n-butyl lithium (48 mL of a 2M solution in hexane) during a period of 15 min. After 15 min ethyl isobutyrate (11.6 g, 0.1mol) was added dropwise during a period of 15 min. After additional 15 min at  $-78^{\circ}\text{C}$ , a precooled solution of 1,4-cyclohexanedione monoethylene ketal in THF (80 mL) was added *via cannula* during a period of 15 min. After stirring for 2 hours at  $-78^{\circ}\text{C}$ , the mixture was allowed to reach room temperature. It was poured onto ammonium chloride solution (100 mL), and extracted with ether (3 x 50 mL). The combined organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated to give 22 g colorless oil; GC-MS (pos.): 273, 255, 181.

15 The crude material was dissolved in pyridine (80 mL), and thionyl chloride (7.5 mL) was added dropwise with cooling in an ice bath. After stirring for 16 hours at room temperature, water (100 mL), and ether (300 mL) was added. The two layers were separated, the organic layer was washed with 1N HCl (3 x 50 mL), brine (2 x 50 mL), dried ( $\text{MgSO}_4$ ), and concentrated to give 18.3 g of ethyl 2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-2-methylpropanoate as a colourless oil.

20

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.22 (t, 3H), 1.30 (s, 6H), 1.74 (t, 2H), 2.18 (m, 2H), 2.33 (s, 2H), 3.96 (m, 4H), 4.13 (q, 2H), 5.50 (s, 1H).

GC-MS (pos.): 255, 181.

*N*-{4-[[[3-(2-ethoxy-1,1-dimethyl-2-oxoethyl)cyclohexyl][4-(trifluoromethoxy)anilino]carbonyl]-amino)methyl]benzoylamino}propionic acid

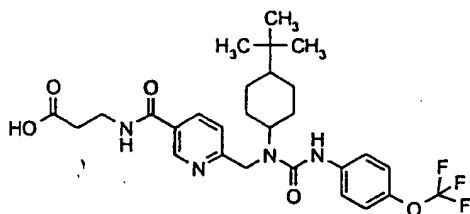
To a solution of ethyl 2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-2-methylpropanoate (694 mg, 3.51 mmol) in THF (5 mL) was added 1N HCl. The mixture was stirred at room temperature for 72 hours, diluted with sodium bicarbonate solution (20 mL), and extracted with ether (3 x 30 mL). The combined organic extracts were dried (MgSO<sub>4</sub>), and concentrated to give 666 mg colourless oil, GC-MS (pos.) 211, 138. The material was dissolved in ethanol (5 mL), and 20 mg Pd/C (10% Pd) was added. The mixture was stirred under a hydrogen atmosphere for 16 hours. The catalyst was filtered off by suction through celite, and the filtrate was concentrated to give 670 mg colorless oil. This material was dissolved in DMF (10 mL), and THF (10 mL), and *N*-[4-(aminomethyl)benzoylamino]propionic acid (700 mg, 3.14mmol) was added followed by sodium triacetoxy borohydride (1.0 g, 4.7 mmol). The mixture was stirred at room temperature for five days, and filtered by suction. The filtrate was concentrated, and coevaporated with methanol and dichloromethane. The residue was dissolved in dichloromethane (5 mL), and triethylamine (1 mL) and 4-trifluoromethoxyphenyl isocyanate (650 mg, 3.20 mmol) was added. After stirring for 16h at room temperature, the mixture was filtered by suction, and the filtrate was concentrated. The residue was dissolved in dichloromethane (100 mL), washed with 1N HCl (2 x 50 mL), brine (50 mL), dried (MgSO<sub>4</sub>), and concentrated. Flash chromatography on silicagel eluting with chloroform/methanol, 9:1 provided the title compound.

<sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 1.06 (s, 1H), 1.09 (s, 6H), 1.22 (t, 2H), 1.46-1.85 (m, 8H), 2.69 (t, 2H), 3.60 (t, 2H), 4.03 – 4.15 (m, 2H), 4.07 (s, 2H), 7.14 (d, 2H), 7.34–7.41 (m, 4H), 7.77 (d, 2H).

MS (APCI, pos.): 622.2

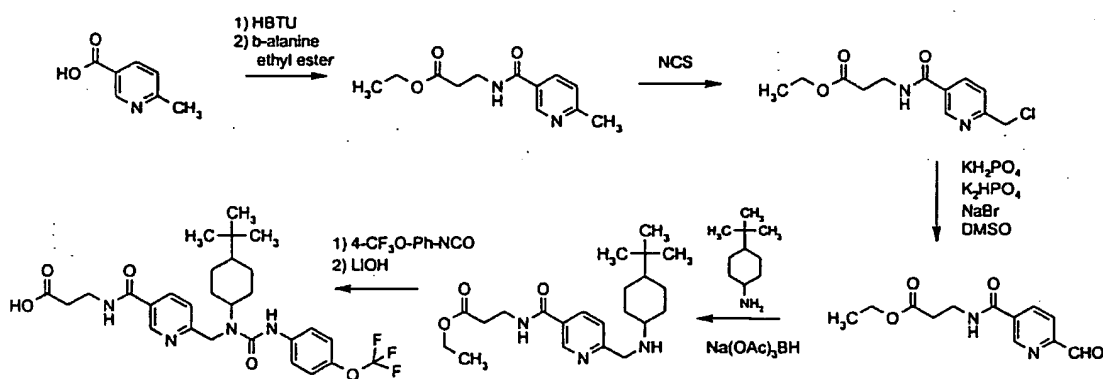
**EXAMPLE 612**

3-((6-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]pyridine-3-carbonyl)amino)propionic acid



5

Reaction scheme:



- 10 To solution of 6-methylnicotinic acid (4.9 g, 35.7 mmol) in DMF (50 mL) was added HBTU (16.2 g, 42.8 mmol) and diisopropylethylamine (11.0 g, 85 mmol). The mixture was stirred at 0°C for 30 min, and β-alanine ethyl ester hydrochloride (6.57 g, 42.8 mmol) was added at 0°C. The reaction was monitored by TLC. The reaction mixture was concentrated in vacuo, and the residue was dissolved in carbon tetrachloride (200 mL). NCS (5.2 g, 38.9 mmol) and a catalytic amount of benzoyl peroxide were added. After refluxing for 2 hours, the solvent was removed in vacuo. Column chromatography on silica gel eluting with hexane/ethyl acetate, 1:1 provided ethyl 3-((6-(chloromethyl)-3-pyridinyl)carbamoyl)aminopropionate as a white solid (2.9 g, overall yield 30%)
- 15
- 20 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ: 1.20 (t, 3H), 2.55 (t, 2H), 3.70 (q, 2H), 4.13 (q, 2H), 4.68 (s, 2H), 7.52 (d, 1H), 7.57 (t, 1H), 8.15 (d, 1H), 8.94 (s, 1H).

To solution of ethyl 3-[[[6-chloromethyl-3-pyridinyl]carbonyl]aminopropanoate (4.0 g, 14.8 mmol) in DMSO (40 mL) was added  $\text{KH}_2\text{PO}_4$  (2.6 g, 14.8 mmol),  $\text{K}_2\text{HPO}_4$  (1.0 g, 7.4 mmol) and sodium bromide (1.5 g, 14.8 mmol). The mixture was heated at 100 °C under nitrogen for 6 hours. TLC showed the starting material was completely consumed. The mixture was  
5 poured onto water (100 mL), and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried ( $\text{MgSO}_4$ ), and concentrated. This material (aldehyde) was used without further purification in the next step.

The crude material (283 mg) was dissolved in dichloromethane (10 mL), and *tert*-butylcyclo-  
10 hexylamine (70 mg, 0.45 mmol) and sodium triacetoxo borohydride (190 mg, 0.89 mmol) were added. The mixture was stirred at room temperature for 16 hours, diluted with dichloromethane (20 mL), washed with sodium bicarbonate solution (20 mL), brine (20 mL), dried ( $\text{MgSO}_4$ ), and concentrated. Flash chromatography on silicagel eluting with chloroform:-methanol:ammonia:water, 90:10:0.5:0.5 provided the desired secondary amine (190 mg); MS  
15 (APCI, pos.): 390.2.

This material was dissolved in chloroform (5 mL), and 4-trifluoromethoxyphenyl isocyanate (150 mg, 0.73 mmol) was added. After stirring at room temperature for 16 hours, the mixture was concentrated. Flash chromatography on silica gel eluting with hexane:ethyl acetate, 1:1  
20 afforded the ethyl ester of the title compound (225 mg).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  0.84 (s, 9H), 0.91-1.84 (m, 9H), 1.27 (t, 3H), 2.66 (t, 2H), 3.74 (q, 2H),  
4.12 (m, 1H), 4.17 (q, 2H), 4.48 (s, 2H), 7.07 (t, 1H), 7.12 (d, 2H), 7.41 (d, 1H), 7.46 (d, 2H),  
8.13 (d, 1H), 8.98 (d, 1H), 9.54 (s, 1H), 9.75 (s, 1H).

25 The above material was dissolved in THF (5 mL), and 1M LiOH (1 mL) was added. After stirring at room temperature for 3 hours, the solution was acidified with 1N HCl to pH = 4, and concentrated. The residue was dissolved in chloroform (20 mL), washed with brine (10 mL), dried ( $\text{MgSO}_4$ ) and concentrated. The title compound crystallized from dichloromethane on  
30 addition of hexane.

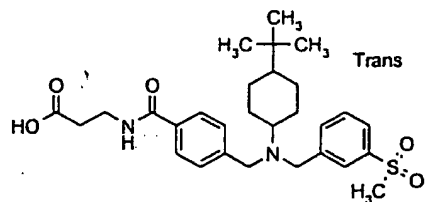
$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  0.82 (s, 9H), 0.93-1.75 (m, 9H), 2.50 (t, 2H), 3.43 (t, 2H), 4.63 (m,  
1H), 4.63 (s, 2H), 7.24 (d, 2H), 7.38 (d, 1H), 7.55 (d, 2H), 8.13 (d, 1H), 8.73 (t, 1H), 8.93 (s,  
1H), 9.05 (s, 1H).



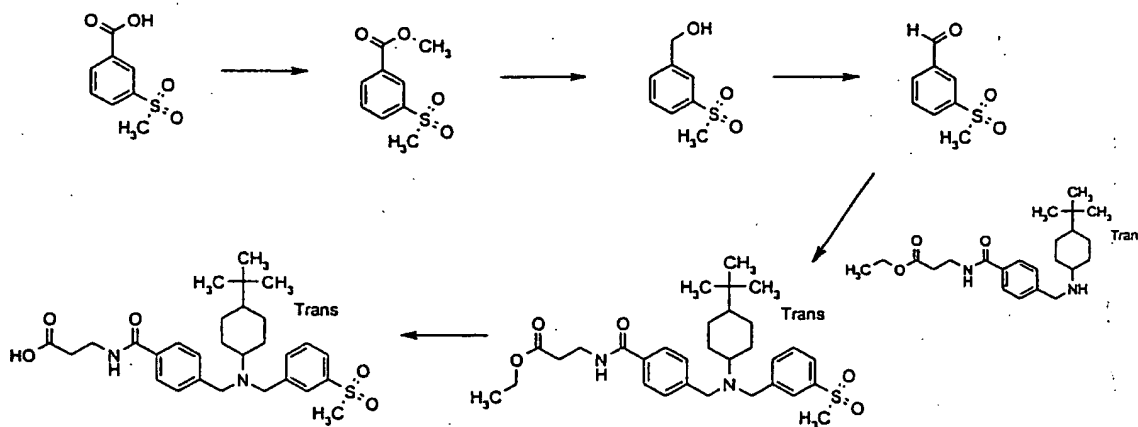
MS (APCI, pos.): 565.1.

### EXAMPLE 613

3-(4-(((trans-4-tert-Butylcyclohexyl)-(3-methylsulfonylbenzyl)amino)methyl)benzoylamino)-propionic acid



Reaction scheme:



To a solution of 3-methylsulfonylbenzoic acid (10 g, 50 mmol) in anhydrous methanol (100 mL) was added conc. sulfuric acid (10 mL). The mixture was refluxed for 4 hours and then concentrated to one-third volume. Water (200 mL) was added, and the mixture was extracted with diethyl ether. The organic extract was washed with 10% sodium carbonate solution, and dried over Na<sub>2</sub>SO<sub>4</sub>. After concentration, 8.6 g (81%) of methyl 3-methylsulfonylbenzoate was obtained.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 3.11 (s, 3H), 4.02 (s, 3H), 7.68 (t, 1H), 8.13 (d, 1H), 8.32 (d, 1H), 6.00 (s, 1H).

To a solution of methyl 3-methylsulfonylbenzoate (4.4 g, 20.3 mmol) in anhydrous THF (100 mL) was added lithium aluminum hydride (7 mL, 1.0 M solution in THF) via syringe at 0°C.

After stirring for 2 hours at room temperature, the mixture was diluted with water, and extracted with diethyl ether. The combined organic extracts were dried ( $\text{MgSO}_4$ ), and concentrated to give 3-methylsulfonyl benzyl alcohol (3.5g, 93%).

5  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 3.02 (s, 3H), 4.68 (s, 2H), 7.47 (t, 1H), 7.57 (d, 1H), 7.75 (d, 1H), 7.89 (s, 1H).

To a solution of 3-methylsulfonyl benzyl alcohol (3.5 g, 28.6 mmol) in dichloromethane (50 mL) was added pyridinium chloro chromate (PCC) (9.1 g, 42.2 mmol). The mixture was  
10 stirred at room temperature for 3 hours. After workup and column chromatography on silica gel eluting with hexane:ethyl acetate, 1:1, 3-methylsulfonylbenzaldehyde was obtained as white solid.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 3.09 (s, 3H), 7.75 (t, 1H), 8.10-8.21 (2d, 2H), 8.40 (s, 1H), 10.11 (s, 1H).

15

To a solution of 3-methylsulfonylbenzaldehyde (0.93 g, 5.1 mmol) and ethyl 3-([4-(*tert*-butyl)-cyclohexyl]amino)methyl)benzoyl]amino)propanoate (1.9 g, 5.1 mmol) in dry DMF (50 mL) was added sodium triacetoxy borohydride (1.6 g, 7.5 mmol) and a catalytic amount of trifluoroacetic acid. The mixture was diluted with water and extracted with ethyl acetate. The  
20 combined organic extracts were dried ( $\text{MgSO}_4$ ), and concentrated. The residue was dissolved in methanol, and saponified by 2M LiOH aqueous solution. After the reaction was complete, the mixture was acidified by 2M HCl, diluted with water, and extracted with ethyl acetate. The combined organic extracts were dried ( $\text{MgSO}_4$ ), and concentrated. The residue was purified by HPLC to give the title compound.

25

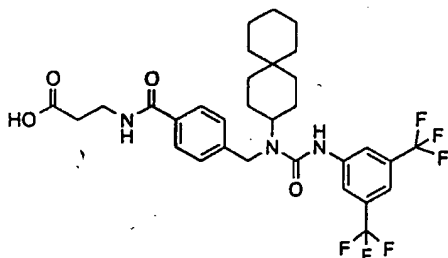
$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.78 (s, 9H), 0.81-0.96 (br, 3H), 1.18-1.39 (br, 2H), 1.71-1.98 (m, 4H), 2.40 (t, 1H), 2.56 (br, 2H), 3.53 (m, 6H), 7.25-7.86 (m, 8H).

LC-MS (APCI, pos.): 529(M+1).

30

**EXAMPLE 614**

3-(4-[3-(3,5-Bis(trifluoromethyl)phenyl)-1-spiro[5.5]undec-3-ylureidomethyl]benzoylamino)-propionic acid



5

The title compound was made similarly as described in example 89.

<sup>1</sup>H NMR (DMSO): δ 12.20 (s br, 1H); 9.05 (s, 1H); 8.48 (t, 1H); 8.22 (s, 2H); 7.72 (d, 2H); 7.55 (s, 1H); 7.32 (d, 2H); 4.65 (s, 2H); 4.08 (t br, 1H); 3.48 (q, 2H); 1.70-1.05 (m, 18H)

10

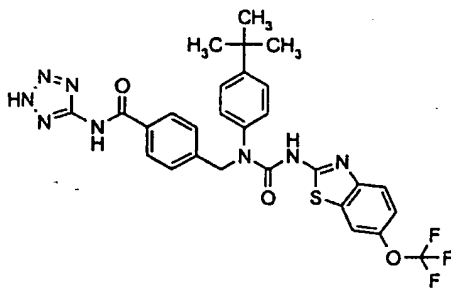
HPLC-MS (Method B): m/z = 628 (M+1). R<sub>t</sub> = 8.30 min.

Spiro[5.5]undecan-3-one was prepared as described by Rice *et al*, *J. Org. Chem.*, **26**, 2637-2640, (1964).

15

**EXAMPLE 615**

4-[1-(4-*tert*-Butylphenyl)-3-(6-trifluoromethoxybenzothiazol-2-yl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



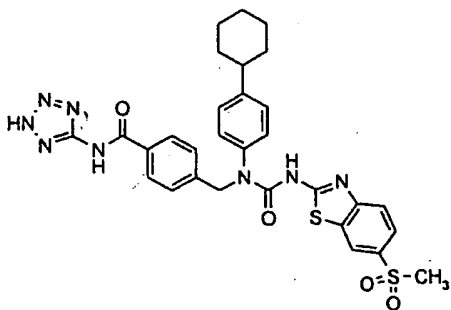
20

The title compound was made similarly as described in example 341.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.30 (9H, s), 5.14 (2H, s), 7.20-7.42, (7H, m), 7.48 (2H, d), 7.98, (1H, s), 8.08 (2H, d), 12.40 (1H, s).

**EXAMPLE 616**

4-[1-(4-Cyclohexylphenyl)-3-(6-methylsulfonylbenzothiazol-2-yl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

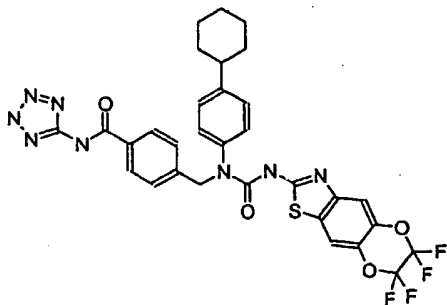
The title compound was made similarly as described in example 341.

HPLC-MS (Method C):  $R_t$  = 5.07 min,  $m/z$  = 631 ( $M+1$ ).

10

**EXAMPLE 617**

4-[1-(4-Cyclohexylphenyl)-3-(6,7-(tetrafluoroethylenedioxy)benzothiazol-2-yl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



15

6,7-(Tetrafluoroethylenedioxy)benzothiazol-2-ylamine was prepared from 6-amino-2,2,3,3-tetrafluoro-1,4-benzodioxene using the general procedure described in Stuckwisch C. G. *J. Am. Chem. Soc.* **1949** 71, 3417:

To a suspension of 6-amino-2,2,3,3-tetrafluoro-1,4-benzodioxene (2 g, 9 mmol) and sodium thiocyanate (3.5 g, 43 mmol) in acetic acid (16 mL) was added dropwise, with stirring, bromine (1.4 g, 9 mmol) dissolved in acetic acid (7 mL) while the temperature was kept

20

below 35°C. After all the bromine had been added the mixture was stirred for 16 hours and then filtered and the residue washed with water. The combined filtrate and the washings were neutralized with concentrated aqueous ammonia. The precipitate was collected on a filter, dried and recrystallized from toluene/hexane to yield 6,7-(tetrafluoroethylenedioxy)-  
 5 benzothiazol-2-ylamine.

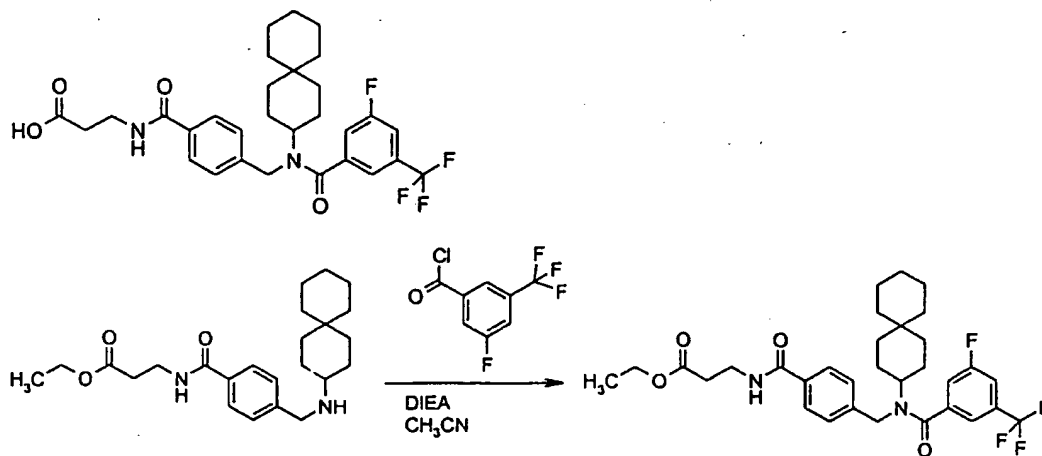
The above 6,7-(tetrafluoroethylenedioxy)benzothiazol-2-ylamine was converted to the title compound using a similar method as described above.

10 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 5.5 (2H, br s), 7.30 (1H, s), 7.37, (1H, s).

HPLC-MS (Method B): R<sub>t</sub> = 8.72 min, m/z = 683 (M + 1).

#### EXAMPLE 618

15 3-(4-[(3-Fluoro-5-trifluoromethylbenzoyl)spiro[5.5]undec-3-yl-amino]methyl)benzoylamino)-propionic acid



3-[4-(Spiro[5.5]undec-3-ylaminomethyl)benzoylamino]propionic acid ethyl ester

20 3-[4-(Spiro[5.5]undec-3-ylaminomethyl)benzoylamino]propionic acid ethyl ester was prepared by reductive alkylation of 3-(4-aminomethyl-benzoylamino)propionic acid ethyl ester with spiro[5.5]undecan-3-one. 3-[4-(Spiro[5.5]undec-3-ylaminomethyl)benzoylamino]propionic acid ethyl ester (200 mg, 499 μmol) was dissolved in acetonitrile (5 mL) and diisopropylethyl-  
 25 amine (170 μL) and cooled on an ice bath. Commercially available 3-fluoro-5-(trifluoromethyl)benzoylchloride (136 mg, 602 μmol) dissolved in acetonitrile (5 mL) was added drop-wise. The reaction was complete within one hour as shown by HPLC. The solvent was

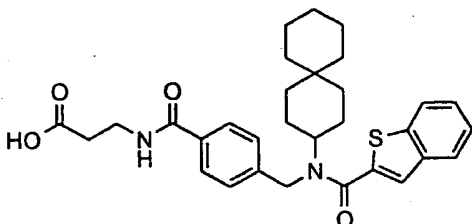
evaporated and water (10 mL) was added to the residue followed by saturated sodium bicarbonate (10 mL). The product was extracted using ethyl acetate (2 x 50 mL). The combined ethyl acetate extracts were washed with water (20 mL) and brine (20 mL). Drying the organic phases over  $\text{MgSO}_4$  and evaporation of the solvent afforded 3-(4-[(3-fluoro-5-trifluoromethyl-benzoyl)spiro[5.5]undec-3-yl-amino]methyl}benzoylamino)propionic acid ethyl ester (295 mg) which was hydrolyzed using sodium hydroxide to afford the title compound.

$^1\text{H}$  NMR (DMSO):  $\delta$  8.45 (t, 1H); 7.75-7.15 (m, 7H); 4.70+4.50 (s+s, 2H); 2.30 (t, 2H); 1.70-0.70 (m, 18-20H).

HPLC-MS (Method D):  $m/z$  = 563 (M+1).  $R_t$  = 3.46 min.

#### EXAMPLE 619

3-(4-[(Benzo[b]thiophene-2-carbonyl)spiro[5.5]undec-3-yl-amino]methyl}benzoylamino)-propionic acid



Prepared similarly as described in example 619.

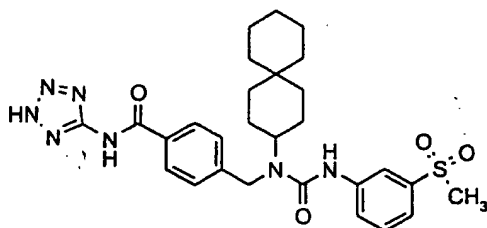
$^1\text{H}$  NMR (DMSO):  $\delta$  12.30 (s br, 1H); 8.51 (t, 1H); 8.05-7.55 (m, 5H); 7.50 (m 4H); 4.70 (s, 2H); 3.30 (s br, 2H); 1.80-0.90 (m, 18H).

HPLC-MS (Method D):  $m/z$  = 533 (M+1).  $R_t$  = 3.51 min.

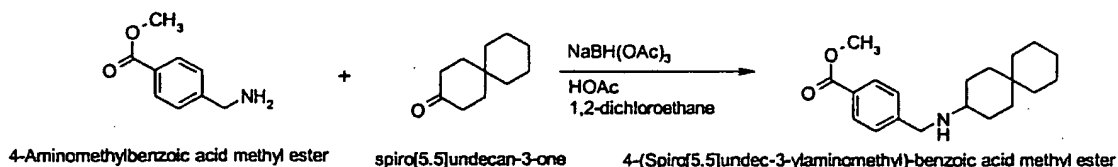
The Benzo[b] thiophene-2-carbonyl chloride was prepared by adding toluene (2 mL), DMF (2 drops) and thionyl chloride (50  $\mu\text{L}$ ) to benzo[b]thiophene-2-carboxylic acid. Heating the mixture to reflux for 5 hours followed by removal of the solvent afforded the crude product, which was used without further purification.

**EXAMPLE 620**

4-[3-(3-Methylsulfonylphenyl)-1-spiro[5.5]undec-3-ylureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide

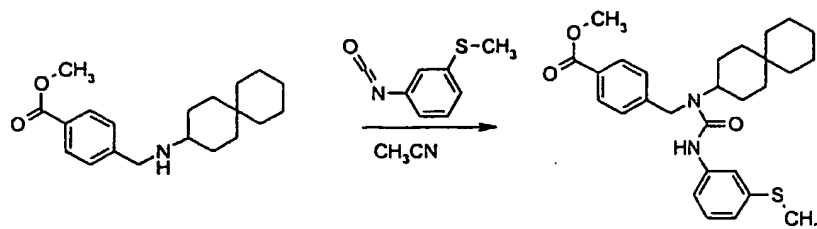


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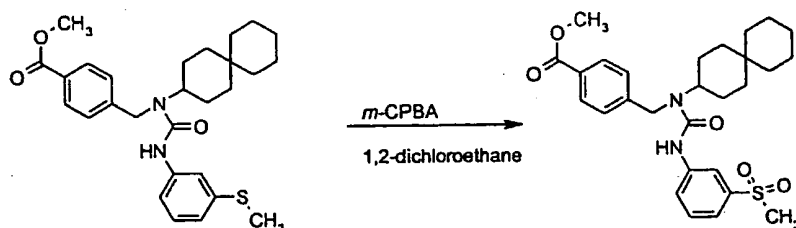
4-Aminomethylbenzoic acid methyl ester hydrochloride (1.45 g, 7.2 mmol) was suspended in 1,2-dichloroethane (50 mL) and added saturated aqueous potassium carbonate. The phases were separated and the aqueous layer was extracted with another portion of 1,2-dichloroethane (50 mL). The combined organic phases were added glacial acetic acid (435  $\mu$ L, 7.6 mmol) followed by spiro[5.5]undecan-3-one (1.2 g, 7.2 mmol). The suspension was stirred for 30 min at 25°C and sodium triacetoxyborohydride (2.27 g, 10.7  $\mu$ mol) was added. After stirring for 2 days at 25°C, water (100 mL) and saturated aqueous potassium carbonate (15 mL) were added. The phases were separated and the aqueous layer was extracted with 1,2-dichloroethane (2 x 100 mL). The combined organic phases were washed with water (100 mL) and brine (100 mL), dried over  $\text{MgSO}_4$  and evaporated to afford 4-(spiro[5.5]undec-3-ylaminomethyl)benzoic acid methyl ester which was used in the subsequent steps without further purification.

20



4-[3-(3-Methylsulfonylphenyl)-1-spiro[5.5]undec-3-ylureidomethyl]-benzoic acid methyl ester

The above 4-(spiro[5.5]undec-3-ylaminomethyl)benzoic acid methyl ester (1.02 g, 3.2 mmol) was added acetonitrile (50 mL) and 3-(methylthio)phenylisocyanate (668 mg, 4 mmol). Upon stirring for 2 days, the reaction appeared incomplete as shown by HPLC, so another portion of 3-(methylthio)phenylisocyanate (240 mg) was added. After stirring for 2 hours the solvent was evaporated. The residue was taken up in dichloromethane (2 mL) and purified by chromatography on silica using dichloromethane as eluent affording 4-[3-(3-methylsulfanylphenyl)-1-spiro[5.5]undec-3-yl-ureidomethyl]benzoic acid methyl ester (680 mg).



4-[3-(3-Methylsulfonyl-phenyl)-1-spiro[5.5]undec-3-yl-ureidomethyl]-benzoic acid methyl ester

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The above 4-[3-(3-methylsulfonylphenyl)-1-spiro[5.5]undec-3-yl-ureidomethyl]benzoic acid methyl ester (550 mg, 1.14 mmol) was dissolved in 1,2-dichloroethane (10 mL) and added *m*-chloroperbenzoic acid (611 mg). The reaction was monitored by HPLC. Upon completion, dichloromethane (20 mL) was added to dissolve any precipitate formed during the reaction. Water (20 mL) was added and the phases were separated. The aqueous phase was extracted with dichloromethane (20 mL) and the combined organic phases were washed with saturated aqueous potassium carbonate (20 mL), water (20 mL) and brine (20 mL), dried over  $\text{MgSO}_4$  and evaporated. The residue was purified on silica (150 g) using a mixture of heptane and ethyl acetate (1:1) as eluent affording 4-[3-(3-methylsulfonylphenyl)-1-spiro[5.5]undec-3-yl-ureidomethyl]benzoic acid methyl ester (362 mg).

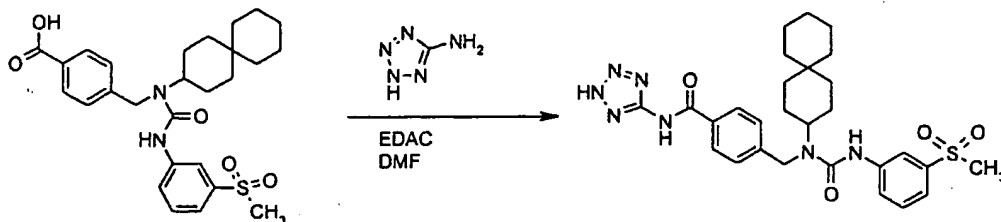
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4-[3-(3-Methylsulfonylphenyl)-1-spiro[5.5]undec-3-yl-ureidomethyl]benzoic acid methyl ester was hydrolyzed to the corresponding carboxylic acid using 3 equiv.  $\text{NaOH(aq)}$  (4M) in dioxane.

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4-[3-(3-Methylsulfonylphenyl)-1-spiro[5.5]undec-3-yl-ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

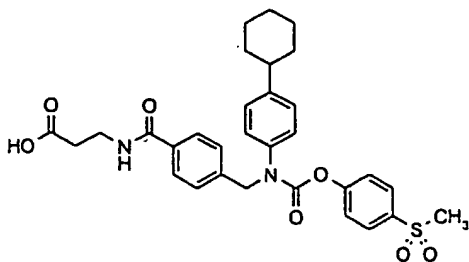
4-[3-(3-Methylsulfonylphenyl)-1-spiro[5.5]undec-3-yl-ureidomethyl]benzoic acid (32.2 mg, 64.6  $\mu$ mol) was dissolved in DMF (1 mL) and added *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDAC) (16.5 mg, 86  $\mu$ mol) and 5-aminotetrazole $\cdot$ H<sub>2</sub>O (16.5 mg, 160  $\mu$ mol). The mixture was stirred at 25°C for 1 day and concentrated *in vacuo*. Brine (5 mL) was added to the residue followed by a mixture of ethanol and chloroform (1:2, 10 mL). The phases were separated and the aqueous layer was extracted with a mixture of ethanol and chloroform (1:2, 2 x 10 mL). The combined organic extracts were dried over MgSO<sub>4</sub> and evaporated. The residue was purified by preparative HPLC affording the title compound.

<sup>1</sup>H NMR (DMSO):  $\delta$  12.30 (s br, 1H); 8.80 (s, 1H); 8.11-8.02 (m, 3H); 7.85 (dt, 1H); 7.55-7.40 (m, 4H); 4.70 (s, 2H); 4.10 (m br 1H); 3.18 (s, 3H); 1.68-1.10 (m, 18H)

HPLC-MS (Method D):  $m/z$  = 566 (M+1).  $R_t$  = 3.03 min.

#### EXAMPLE 621

3-(4-[[[4-(4-Cyclohexylphenyl)-(4-(methylsulfonyl)phenoxy)carbonyl]amino]methyl]benzoyl-amino)propionic acid



20

3-(4-[[[4-(4-Cyclohexylphenyl)-(4-(methylsulfonyl)phenoxy)carbonyl]amino]methyl]benzoyl-amino)propionic acid (0.05 mmol) assembled on 2-chlorotrityl resin (50 mg) as described in general procedure (Q) was treated overnight with 3-chloroperbenzoic acid (34.5 mg, 0.200 mmol) in NMP (0.50 mL). The solvent was drained off, and the resin washed with DMF (3 x

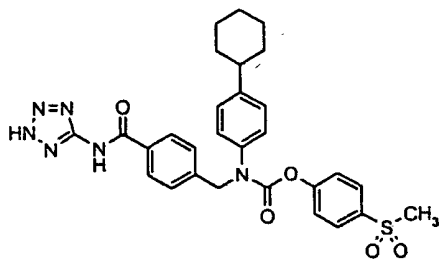
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followed by dichloromethane (10 x). The product was cleaved from the support using 5% TFA in dichloromethane as described in general procedure (Q), and the pure product obtained as crystals after removal of solvent using speed vacuum. Yield: 5.0 mg.

5 HPLC-MS (method B):  $m/z$  = 579,  $R_t$  = 6.55 min.

#### EXAMPLE 622

(4-Cyclohexylphenyl)-[4-(2H-tetrazol-5-ylcarbamoyl)benzyl]carbamic acid 4-(methylsulfonyl)-phenyl ester



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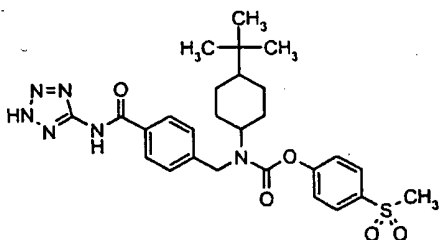
Prepared as described above in example 621. Yield: 15 mg.

HPLC-MS (method B):  $m/z$  = 575,  $R_t$  = 6.88 min.

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#### EXAMPLE 623

(4-tert-Butylcyclohexyl)-[4-(2H-tetrazol-5-ylcarbamoyl)benzyl]carbamic acid 4-(methylsulfonyl)phenyl ester



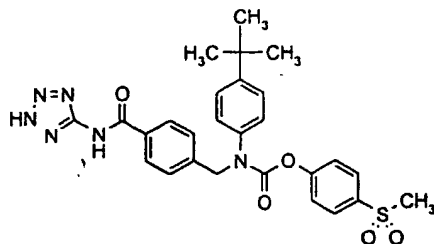
20

Prepared as described above in example 621. Yield: 15 mg.

HPLC-MS (method B):  $m/z$  = 555,  $R_t$  = 7.07 min.

**EXAMPLE 624**

(4-tert-Butylphenyl)-[4-(2H-tetrazol-5-ylcarbamoyl)benzyl]carbamic acid 4-(methylsulfonyl)-phenyl ester

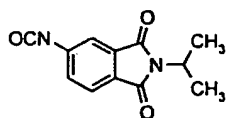


5

Prepared as described above in example 621. Yield: 15 mg.

HPLC-MS (method B):  $m/z$  = 549,  $R_t$  = 6.35 min.

10 Preparation of starting materials for phthalimide compounds of the invention:

**N-Isopropylphthalimide-4-isocyanate**

15 Step 1: 4-Nitroisophthalimide (25.0 g, 130.0 mmol) was dissolved in DMF (250 mL). Isopropyl bromide (61.0 mL, 650 mmol) and potassium carbonate (36.0 g, 260 mmol) were added and the mixture was heated to 60°C overnight. Water (1.0 L) was added, and the precipitate formed was collected by filtration, washed twice with water and dried overnight in a vacuum oven to afford 21.3 g (70%) of pure N-isopropyl-4-nitrophthalimide.

20

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.42 ppm (d, 6H); 4.44 (m, 1H); 8.07 (d, 1H); 8.45 (s, 1H); 8.61 (d, 1H).

25 Step 2: N-Isopropyl-4-nitrophthalimide (10.0 g, 43.0 mmol) was dissolved in a mixture of THF (200 mL) and DMF (100 mL). 10% Palladium catalyst on carbon (1.0 g, 50% wet weight) was added and the mixture was hydrogenated in a low-pressure apparatus (1 atm.) overnight. The catalyst was then removed by filtering the mixture through a short pad of celite. The fil-

trate was evaporated to dryness to afford a quantitative yield (8.70 g) of pure *N*-isopropyl-4-aminophthalimide.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.46 ppm (d, 6H); 4.47 (m, 1H); 6.82 (dd, 1H); 7.00 (d, 1H); 7.55 (d, 1H).

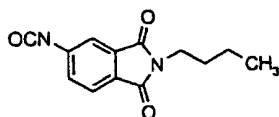
5

Step 3: *N*-Isopropyl-4-aminophthalimide (9.50 g, 47 mmol) was dissolved in THF (200 mL). While stirring, a solution of HCl in ethyl acetate (90 mL, 3.5 M, 315 mmol) was slowly added to form the anilinium hydrochloride. Solvent was removed, and the precipitate was re-suspended and evaporated twice from THF. The solid residue was then suspended in toluene (250 mL), and trichloromethyl chloroformate (60 mL, 500 mmol) was added. The suspension was heated to reflux and after 2 hours, a clear solution was obtained. Reflux was continued overnight. The solution was allowed to cool to room temperature before the solvent was removed by evaporation. The crystalline residue was stripped with toluene (2 x 200 mL) and acetonitrile (2 x 200 mL), and the obtained *N*-isopropylphthalimide-4-isocyanate was used for subsequent reactions without further purification. Yield : 10.7 g (99%).

15

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.49 ppm (d, 6H); 4.50 (m, 1H); 7.37 (d, 1H); 7.51 (s, 1H); 7.76 (d, 1H).

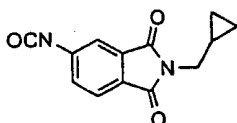
*N*-Butylphthalimide-4-isocyanate



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This material was prepared similarly as described for *N*-isopropylphthalimide-4-isocyanate.

*N*-(Cyclopropylmethyl)phthalimide-4-isocyanate



25

Step 1: 4-Nitrophthalimide (6.15 g, 32.0 mmol) was dissolved in DMF (60 mL). Cyclopropylmethyl bromide (9.3 mL, 96 mmol) and potassium carbonate (8.85 g, 64.0 mmol) were added and the mixture was heated to 100°C for 4 hours. The mixture was allowed to cool to room temperature, and then partitioned between water (500 mL) and ethyl acetate (400 mL). The organic phase was collected, dried with  $\text{Na}_2\text{SO}_4$ , filtered and taken to dryness using rotary

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evaporation. The residue was dried overnight in a vacuum oven to afford 6.49 g (82%) of pure *N*-cyclopropylmethyl-4-nitrophthalimide as a powder.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.36 ppm (d, 2H); 0.50 (d, 2H); 1.12 (m, 1H); 3.51 (d, 2H); 8.13 (d, 1H); 8.50 (s, 1H); 8.62 (d, 1H).

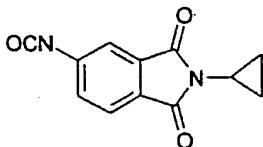
Step 2: *N*-Cyclopropylmethyl-4-nitrophthalimide (6.0 g, 24 mmol) in methanol (200 mL) was added dropwise over 30 min to a solution of sodium dithionite (27.0 g, 156 mmol) and sodium carbonate (13.0 g, 125 mmol) in water (200 mL) while the temperature was maintained at 70°C. The mixture was stirred at 70°C for an additional 50 min before it was allowed to cool to room temperature. The reaction volume was then reduced to one-third by rotary evaporation. Water (400 mL) was added, and the suspension extracted with ethyl acetate (2 x 450 mL). The combined organic solutions were dried with anhydrous MgSO<sub>4</sub>. Solvent was then removed by rotary evaporation to afford 2.52 g (49%) of pure *N*-cyclopropylmethyl-4-aminophthalimide as a powder.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): 0.25 ppm (d, 2H); 0.44 (d, 2H); 1.05 (m, 1H); 3.35 (d, 2H); 6.46 (s, 2H); 6.78 (d, 1H); 6.92 (s, 1H); 7.46 (d, 1H).

HPLC-MS (method B): *m/z* = 217, *R*<sub>t</sub> = 4.65 min.

Step 3: *N*-Cyclopropylmethyl-4-aminophthalimide (2.5 g, 11.6 mmol) was suspended in toluene (30 mL) and bis(trichloromethyl) carbonate (2.28 g, 7.71 mmol) was added. The mixture was heated to reflux under an inert atmosphere for 2 hours. The reaction mixture was cooled on an ice bath before filtering. The filtrate was then taken to dryness, and the oily residue suspended in petroleum ether (40 mL). The pure title material was obtained as a precipitate, which was collected by filtration and washed twice with cold petroleum ether to afford 1.50 g (54%) of *N*-(cyclopropylmethyl)phthalimide-4-isocyanate.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.37 ppm (m, 2H); 0.50 (m, 2H); 1.19 (m, 1H); 3.54 (d, 2H); 7.89 (d, 1H); 7.54 (s, 1H); 7.81 (d, 1H).

N-Cyclopropylphthalimide-4-isocyanate

5 Step 1: 4-Nitrophthalic anhydride (5.60 g, 28.9 mmol) was dissolved in THF (50 mL), and cyclopropylamine (2.10 mL, 30 mmol) was added slowly while stirring under an inert atmosphere. After 30 min, a suspension was obtained. Triethylamine (8.2 mL, 60 mmol) and diisopropylcarbodiimide (5.50 mL, 35 mmol) were added followed by DMF (100 mL). The reaction mixture was then heated to 70°C for 48 hours. The mixture was cooled to room temperature and the reaction volume was reduced to one-tenth of the original volume by rotary evaporation  
10 in vacuo. The precipitated *N,N'*-diisopropylurea was removed by filtration, and water (40 mL) was added to the mother liquor resulting in formation of a precipitate. The precipitate was collected by filtration and dried overnight in a vacuum oven to give 6.02 g (90%) of *N*-cyclopropyl-4-nitrophthalimide.

15 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.92 ppm (m, 4H); 2.71 (s, 1H); 8.07 (d, 1H); 8.44 (d, 1H); 8.58 (dd, 1H).

HPLC-MS (method B): *m/z* = 233, *R*<sub>t</sub> = 4.67 min.

20 Step 2: *N*-Cyclopropyl-4-nitrophthalimide (10.0 g, 43.0 mmol) was dissolved in ethanol (200 mL). Tin (II) chloride dihydrate (49.0 g, 215 mmol) was added, and the mixture was heated to reflux overnight. After cooling, the mixture was poured over crushed ice (1.0 L), and pH adjusted to 6.5 using 1 N NaOH. The mixture was passed through a small bed of celite, and the filtrate was subsequently extracted with ethyl acetate (1.2 L). The organic phase was dried  
25 using anhydrous MgSO<sub>4</sub>, and solvent was removed by rotary evaporation in vacuo, to afford crystalline *N*-cyclopropyl-4-aminophthalimide. Yield: 6.0 g (69%).

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.85 ppm (m, 4H); 2.55 (m, 1H); 6.41 (bs, 2H); 6.77 (d, 1H); 6.86 (d, 1H); 7.44 (dd, 1H).

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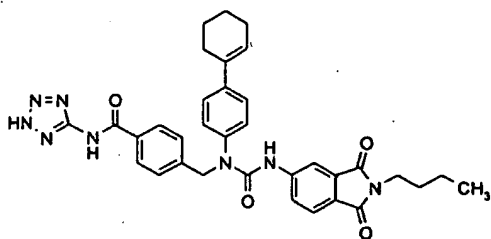
Step 3: *N*-Cyclopropyl-4-aminophthalimide (3.00 g, 15.0 mmol) was dissolved in THF (50 mL). A 3.5 N HCl – ethyl acetate solution (26 mL, 90.0 mmol) was added resulting in immediate precipitation of the hydrochloride salt. Solvent was removed, and the crystalline residue

suspended in toluene (50 mL). Trichloromethyl chloroformate (22.0 mL, 180 mmol) was added and the suspension was heated to reflux. After 2 hours a clear solution was obtained. The solution was heated to reflux overnight. After cooling, solvent was removed and the residue was stripped twice with acetonitrile to remove traces of hydrochloric acid. The crystalline residue (*N*-cyclopropylphthalimide-4-isocyanate) was sufficiently pure for further synthesis.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.10 ppm (m, 4H); 2.66 (m, 1H); 7.39 (d, 1H); 7.75 (d, 1H); 7.78 (dd, 1H).

#### EXAMPLE 625

10 4-[3-(*N*-Butylphthalimid-4-yl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



4-[(4-Cyclohex-1-enylphenylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide (0.5 mmol) assembled on 2-chlorotrityl resin (500 mg) as described under general procedure (Q) was treated with a solution of *N*-butylphthalimide-4-isocyanate (1220 mg, 5.0 mmol) in NMP/1,2-dichloropropane (1:5, 10 mL) for 48 hours. Solvent was drained and the resin was washed with DMF (3 x) and dichloromethane (10 x). Standard cleavage with 10% TFA/dichloromethane and evaporation of solvent afforded a powder, which was further purified by recrystallization from acetonitrile to afford 227 mg (73%) of the title compound.

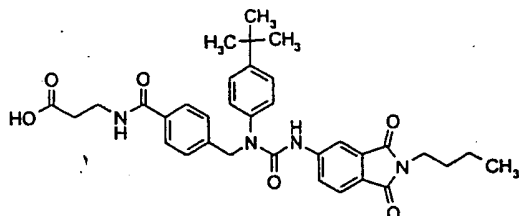
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 0.89 ppm (t, 3H); 1.28 (q, 2H); 1.57 (m, 4H); 1.72 (m, 2H); 2.17 (m, 2H); 2.45 (m, 2H); 3.54 (t, 2H); 5.04 (s, 2H); 6.20 (t, 1H); 7.25 (d, 2H); 7.41 (d, 2H); 7.48 (d, 2H); 7.72 (d, 1H); 7.84 (dd, 1H); 8.01 (d, 1H); 8.03 (d, 2H); 8.92 (s, 1H); 12.35 (s, 1H).

25

HPLC-MS (method B): *m/z* = 620, *R*<sub>t</sub> = 5.15 min.

### EXAMPLE 626

3-{4-[3-(*N*'-Butylphthalimid-4-yl)-1-(4-*tert*-butylphenyl)ureidomethyl]benzoylamino}propionic  
acid



Prepared as described above using resin bound 3-{4-[(4-*tert*-butylphenylamino)methyl]-benzoylamino}propionic acid. An oil was obtained after TFA cleavage and evaporation of solvent. The oil was taken up in ethanol (3 mL) and added dropwise to water (25 mL) while stirring. A fine white powder was obtained which was collected by filtration and dried overnight in a vacuum oven to afford 231 mg (77%) of the title compound.

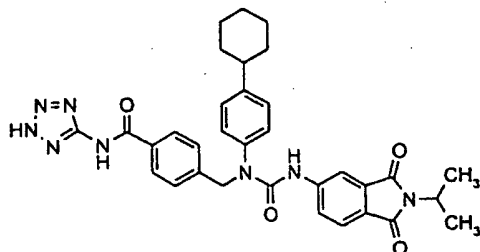
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): 0.89 ppm (t, 3H); 1.26 (s, 9H); 1.28 (m, 2H); 1.54 (m, 2H); 2.48 (m, 2H); 3.42 (m, 2H); 3.53 (t, 2H); 7.20 (d, 2H); 7.35 (d, 2H); 7.39 (d, 2H); 7.71 (d, 1H); 7.76 (d, 2H); 7.80 (dd, 1H); 8.03 (d, 1H); 8.47 (t, 1H); 8.95 (s, 1H); 12.25 (bs, 1H).

HPLC-MS (method B):  $m/z$  = 599,  $R_t$  = 7.15 min.

The following examples 627 to 645 were prepared in a similar way:

### EXAMPLE 627

4-[1-(4-Cyclohexylphenyl)-3-(N-isopropylphthalimid-4-yl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide

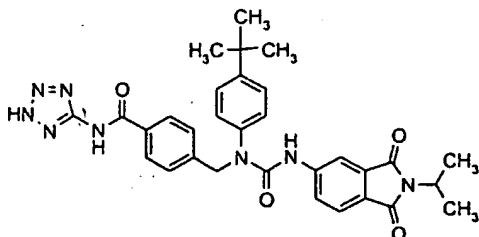


HPLC-MS (method B):  $m/z$  = 607.0,  $R_t$  = 7.62 min.



**EXAMPLE 628**

4-[1-(4-*tert*-Butyl-phenyl)-3-(*N'*-isopropylphthalimid-4-yl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide

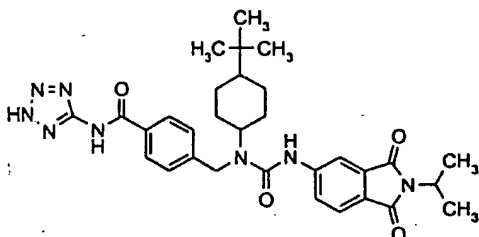


5

HPLC-MS (method B):  $m/z$  = 581.0,  $R_t$  = 7.62 min.

**EXAMPLE 629**

10 4-[1-(4-*tert*-Butylcyclohexyl)-3-(*N'*-isopropylphthalimid-5-yl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide

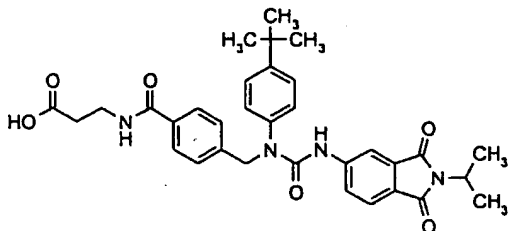


HPLC-MS (method B):  $m/z$  = 531.0,  $R_t$  = 7.52 min. (*cis*-isomer);  $R_t$  = 7.62 min. (*trans*-isomer).

15

**EXAMPLE 630**

3-{4-[1-(4-*tert*-Butylphenyl)-3-(*N'*-isopropylphthalimid-4-yl)ureidomethyl]benzoylamino}-propionic acid

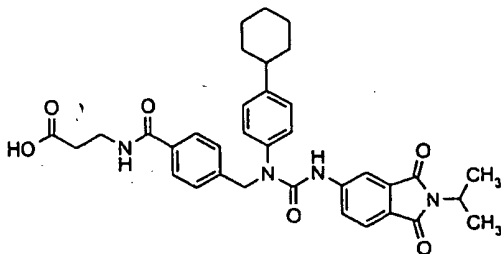


20

HPLC-MS (method B):  $m/z$  = 585.0,  $R_t$  = 6.83 min.

**EXAMPLE 631**

3-[4-[1-(4-Cyclohexyl-phenyl)-3-(*N'*-isopropylphthalimid-4-yl)ureidomethyl]benzoylamino]-propionic acid

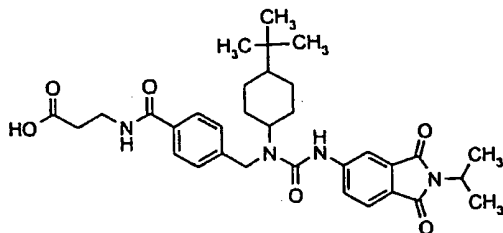


5

HPLC-MS (method B):  $m/z$  = 611.0,  $R_t$  = 7.42 min.

**EXAMPLE 632**

10 3-[4-[1-(4-*tert*-Butylcyclohexyl)-3-(*N'*-isopropylphthalimid-4-yl)ureidomethyl]benzoylamino]-propionic acid

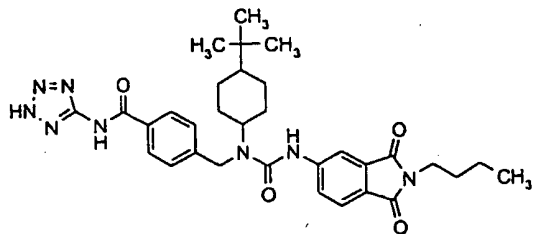


HPLC-MS (method B):  $m/z$  = 591.0,  $R_t$  = 7.35 min. (*cis*-isomer);  $R_t$  = 7.45 min. (*trans*-isomer).

15

**EXAMPLE 633**

4-[1-(4-*tert*-Butylcyclohexyl)-3-(*N'*-butylphthalimid-4-yl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide

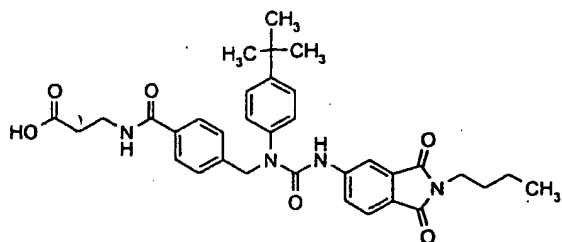


20

HPLC-MS (method B):  $m/z$  = 601.0,  $R_t$  = 7.68 min. (*cis*-isomer);  $R_t$  = 7.83 min. (*trans*-isomer).

**EXAMPLE 634**

3-[4-[3-(*N'*-Butylphthalimid-4-yl)-1-(4-*tert*-butylphenyl)ureidomethyl]benzoylamino]propionic acid

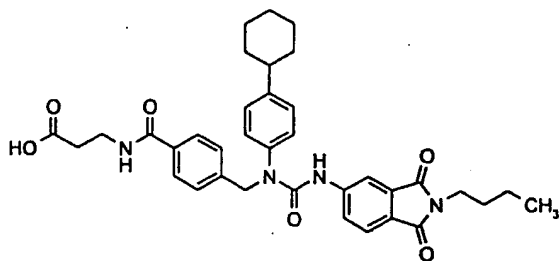


5

HPLC-MS (method B):  $m/z$  = 599.0,  $R_t$  = 7.15 min.

**EXAMPLE 635**

3-[4-[3-(*N'*-Butylphthalimid-4-yl)-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino]propionic acid

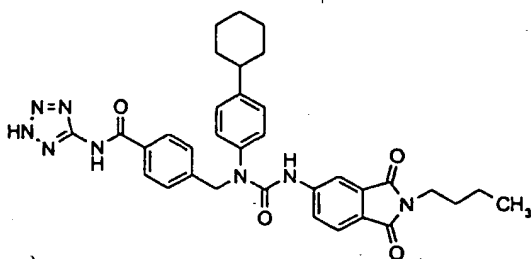


HPLC-MS (method B):  $m/z$  = 625.0,  $R_t$  = 7.68 min.

15

**EXAMPLE 636**

4-[3-(*N'*-Butylphthalimid-4-yl)-1-(4-cyclohexylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



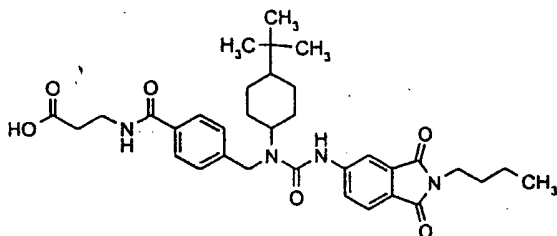
20

HPLC-MS (method B):  $m/z$  = 621.0,  $R_t$  = 7.92 min.

**EXAMPLE 637**

3-[4-[1-(4-*tert*-Butylcyclohexyl)-3-(*N'*-butylphthalimid-4-yl)ureidomethyl]benzoylamino]-

5 propionic acid

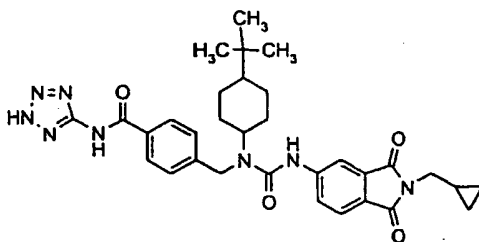


HPLC-MS (method B):  $m/z$  = 605.0,  $R_t$  = 7.58 min. (*cis*-isomer);  $R_t$  = 7.68 min. (*trans*-isomer).

10 **EXAMPLE 638**

4-[1-(4-*tert*-Butylcyclohexyl)-3-(*N'*-[cyclopropylmethyl]phthalimid-4-yl)ureidomethyl]-*N*-(2*H*-

tetrazol-5-yl)benzamide

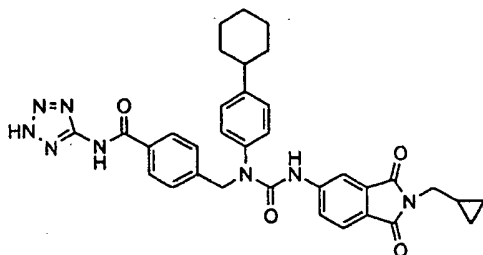


15 HPLC-MS (method B):  $m/z$  = 599.0,  $R_t$  = 7.52 min. (*cis*-isomer);  $R_t$  = 7.72 min. (*trans*-isomer).

**EXAMPLE 639**

4-[1-(4-Cyclohexylphenyl)-3-(*N'*-[cyclopropylmethyl]phthalimid-4-yl)ureidomethyl]-*N*-(2*H*-

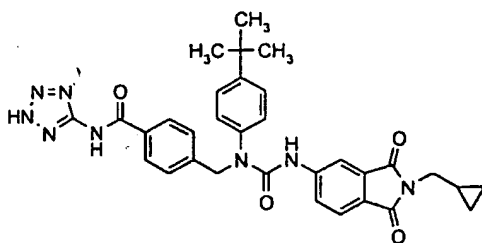
tetrazol-5-yl)benzamide



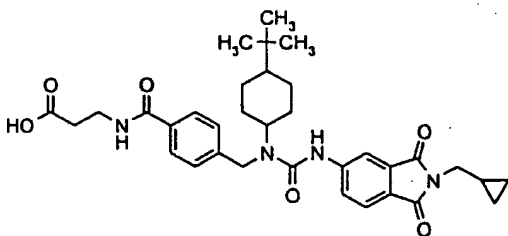
493

HPLC-MS (method B):  $m/z$  = 619.0,  $R_t$  = 7.73 min.**EXAMPLE 640**

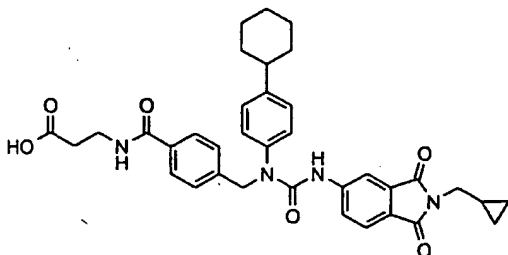
4-[1-(4-*tert*-Butylphenyl)-3-(*N'*-[cyclopropylmethyl]phthalimid-4-yl)ureidomethyl]-*N*-(2*H*-  
5 tetrazol-5-yl)benzamide

HPLC-MS (method B):  $m/z$  = 593.0,  $R_t$  = 7.20 min.**EXAMPLE 641**

3-[4-[1-(4-*tert*-Butylcyclohexyl)-3-(*N'*-[cyclopropylmethyl]phthalimid-4-yl)ureidomethyl]-  
benzoylamino]propionic acid

HPLC-MS (method B):  $m/z$  = 603.0,  $R_t$  = 7.38 min.**EXAMPLE 642**

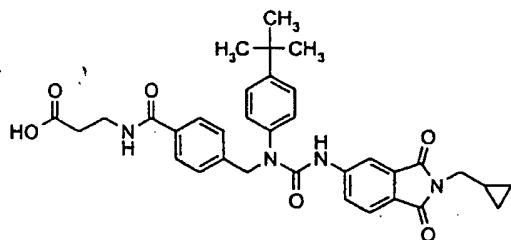
3-[4-[3-(*N'*-[Cyclopropylmethyl]phthalimid-4-yl)-1-(4-cyclohexylphenyl)ureidomethyl]-  
benzoylamino]propionic acid



HPLC-MS (method B):  $m/z$  = 623.0,  $R_t$  = 7.45 min.

**EXAMPLE 643**

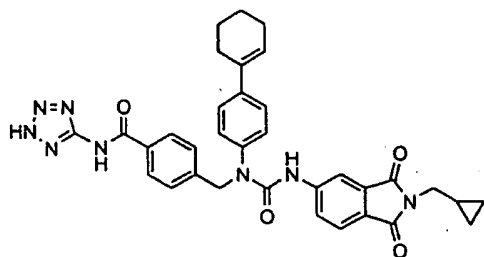
3-[4-[3-(*N'*-[Cyclopropylmethyl]phthalimid-4-yl)-1-(4-*tert*-butylphenyl)ureidomethyl]benzoyl-  
amino}propionic acid



HPLC-MS (method B):  $m/z$  = 597.0,  $R_t$  = 6.89 min.

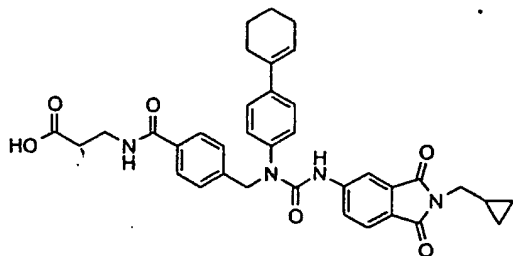
**EXAMPLE 644**

4-[3-(*N'*-[Cyclopropylmethyl]phthalimid-4-yl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-*N*-(2H-  
tetrazol-5-yl)benzamide



**EXAMPLE 645**

3-{4-[1-(4-Cyclohex-1-enyl)phenyl]-3-(*N'*-[cyclopropylmethyl]phthalimid-4-yl)ureidomethyl}-benzoylamino}propionic acid



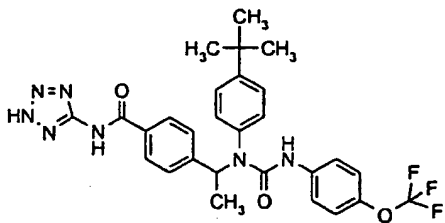
5

HPLC-MS (method B):  $m/z$  = 621.0,  $R_t$  = 7.32 min.

**EXAMPLE 646**

4-{1-[1-(4-*tert*-Butyl)phenyl]-3-(4-trifluoromethoxyphenyl)ureido]ethyl}-*N*-(2*H*-tetrazol-5-yl)benzamide

10



Step 1: 4-Acetylbenzoic acid (4.00 g, 24.4 mmol), 5-aminotetrazole monohydrate (3.00 g, 2.91 mmol) and ethyl dimethylaminopropyl carbodiimide hydrochloride (7.00 g, 3.55 mmol) were dissolved in DMF (25 mL) and stirred at ambient temperature for 48 hours. The reaction mixture was poured into ice-water, and the precipitate collected by filtration to afford 5.50 g (98%) of pure 4-acetyl-*N*-(2*H*-tetrazol-5-yl)benzamide after drying overnight in a vacuum oven.

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  2.64 ppm (s, 3H); 8.12 (d, 2H), 8.20 (d, 2H), 12.60 (bs, 1H).

Step 2: 4-Acetyl-*N*-(2*H*-tetrazol-5-yl)benzamide (1.00 g, 4.32 mmol) and 4-*tert*-butylaniline were dissolved in THF (15 mL). Triethylamine (2.1 mL, 15.0 mmol) was added and the mixture was cooled to 0°C on an ice bath. Neat titanium tetrachloride (0.25 mL, 2.25 mmol) was added dropwise using a syringe assuring that the temperature was maintained close to 0°C. The mixture was then stirred overnight at room temperature. A solution of sodium cyano-

25

borohydride (0.88 g, 14 mmol) in methanol (10 mL) was slowly added, and the reaction mixture stirred for a further 60 min. The reaction mixture was then poured into ice water (100 mL) and pH adjusted to 2 using 1M aqueous hydrochloric acid. The crude product was collected by filtration and dried in a vacuum oven overnight. The crude product was taken up in  
5 DMF/ethyl acetate (1:1, 5 mL) and passed through a silica gel column using 5% acetic acid/ethyl acetate as eluent. Pure fractions were pooled and evaporated to dryness. The yield of 4-[1-(4-*tert*-butylphenylamino)ethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide was 1.12 g (71%).

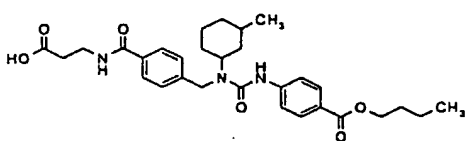
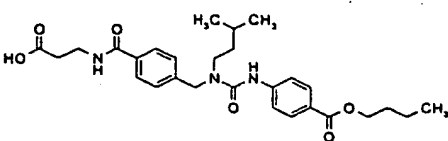
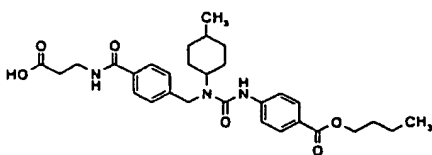
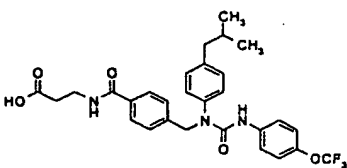
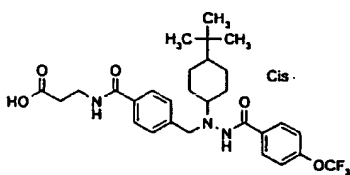
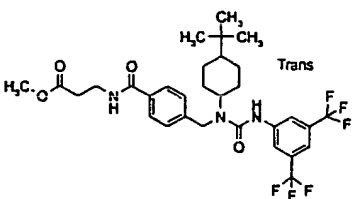
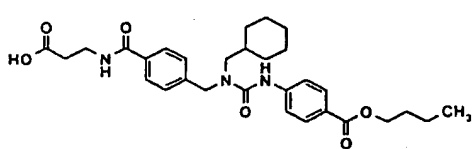
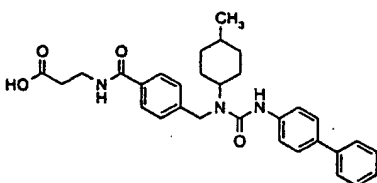
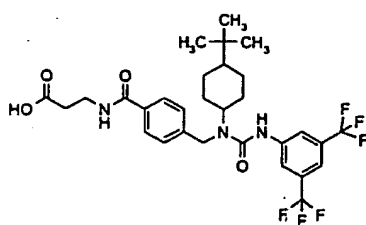
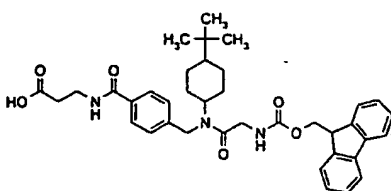
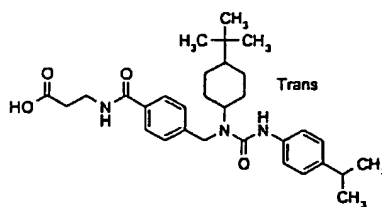
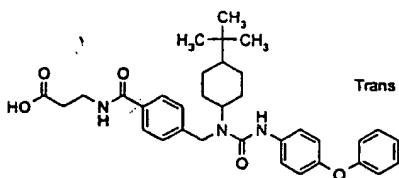
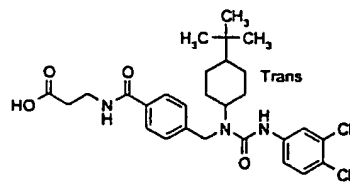
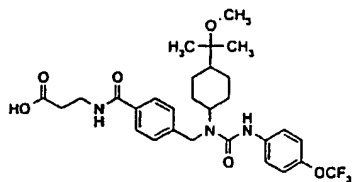
<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 1.15 ppm (s, 9H); 1.43 (d, 3H); 4.52 (q, 1H); 6.09 (bs, 1H); 6.41 (d,  
10 2H); 7.00 (d, 2H); 7.56 (d, 2H); 8.04 (d, 2H); 12.30 (s, 1H).

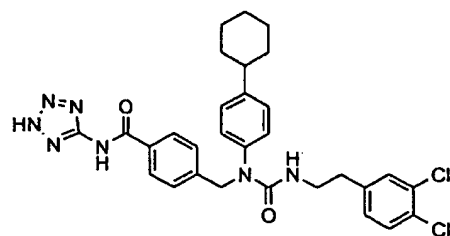
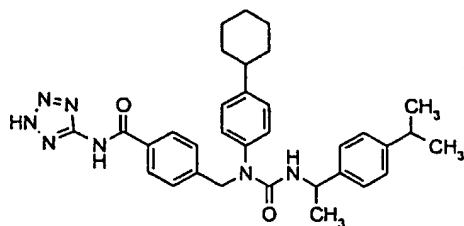
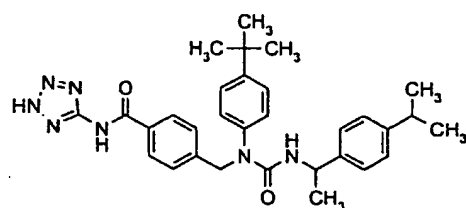
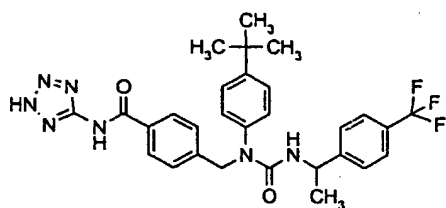
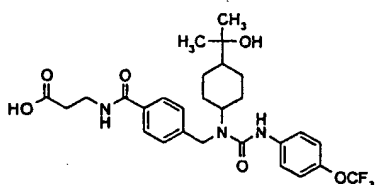
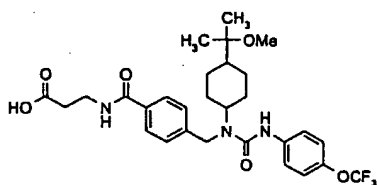
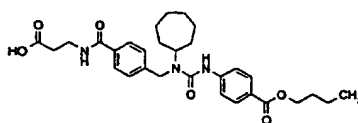
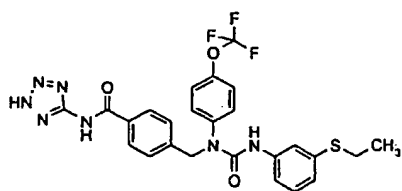
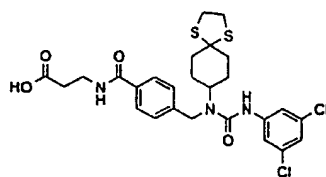
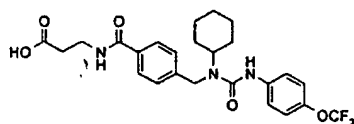
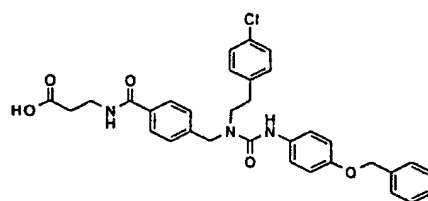
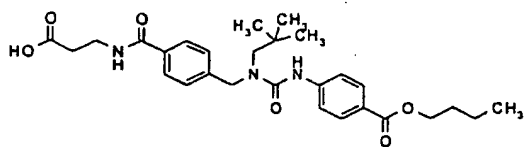
Step 3: 4-[1-(4-*tert*-Butylphenylamino)ethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide (100 mg, 0.28 mmol) and 4-trifluoromethoxyphenyl isocyanate (70 mg, 0.30 mmol) was dissolved in DMF (0.6 mL) and the solution was heated to 80°C for 3 hours. The mixture was cooled to room  
15 temperature and subsequently taken to dryness using rotary evaporation. The residual oil was dissolved in a minimum of DMF/acetonitrile (1:1), and submitted to preparative HPLC purification. Pure fractions were pooled and concentrated to dryness to afford 10 mg (8%) of the title compound.

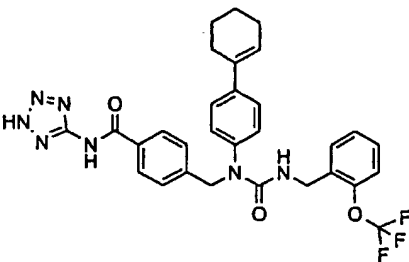
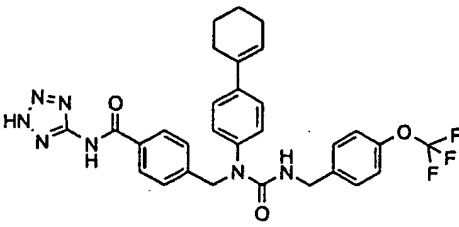
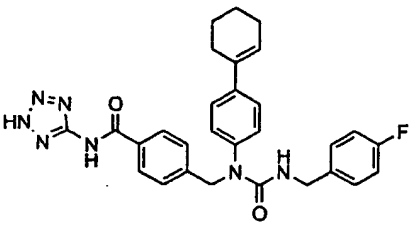
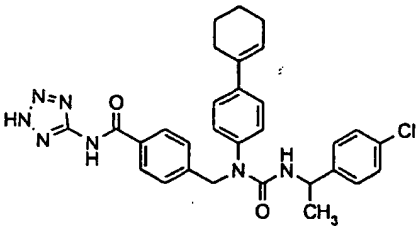
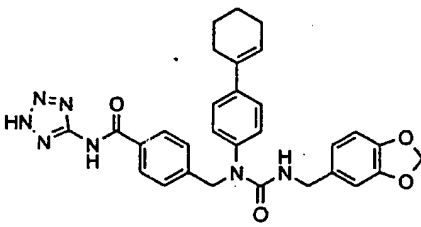
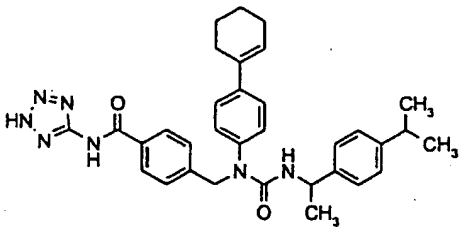
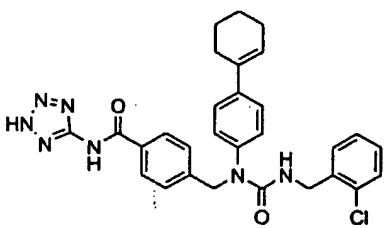
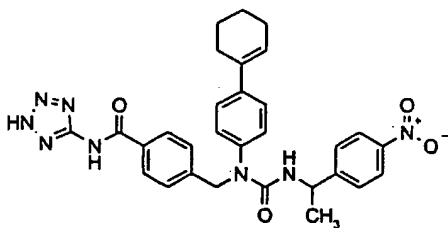
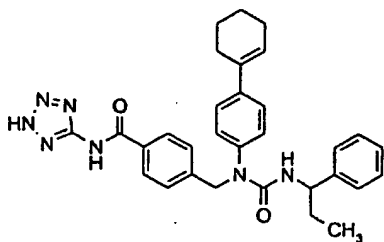
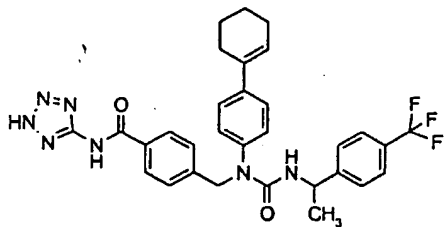
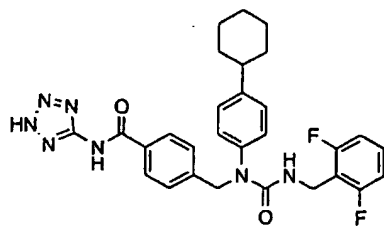
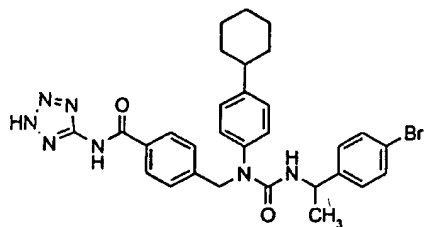
20 HPLC-MS (method B): *m/z* = 568.0, *R*<sub>t</sub> = 5.31 min.



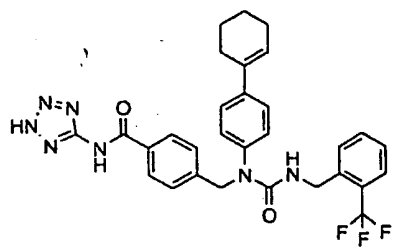
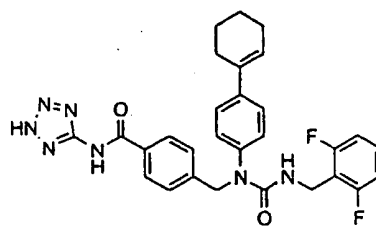
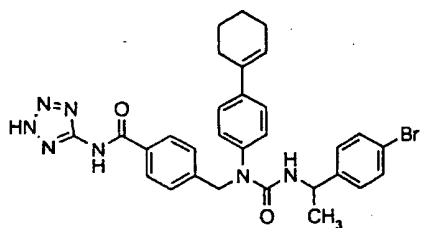
Furthermore, the following compounds according to the invention are preferred:



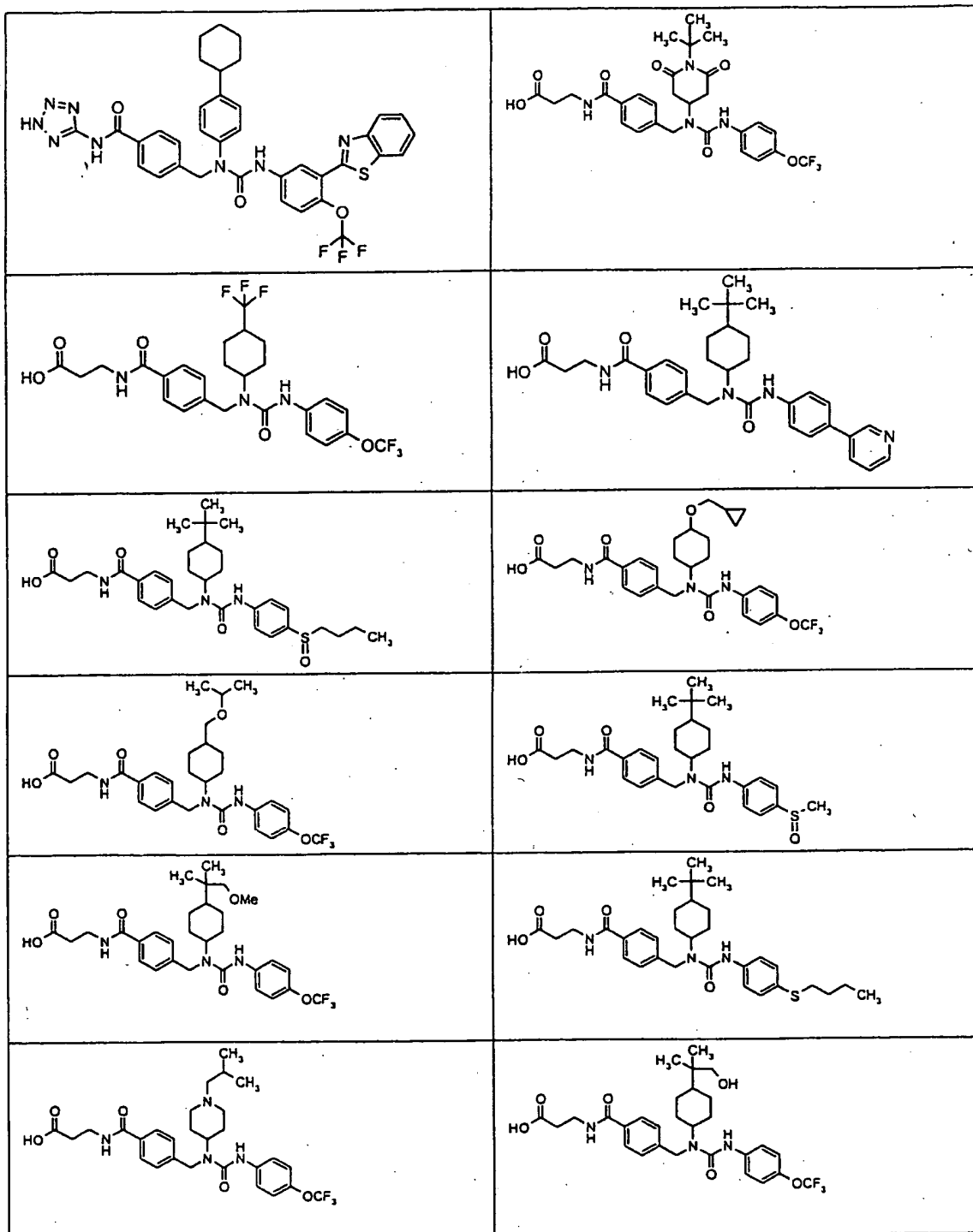


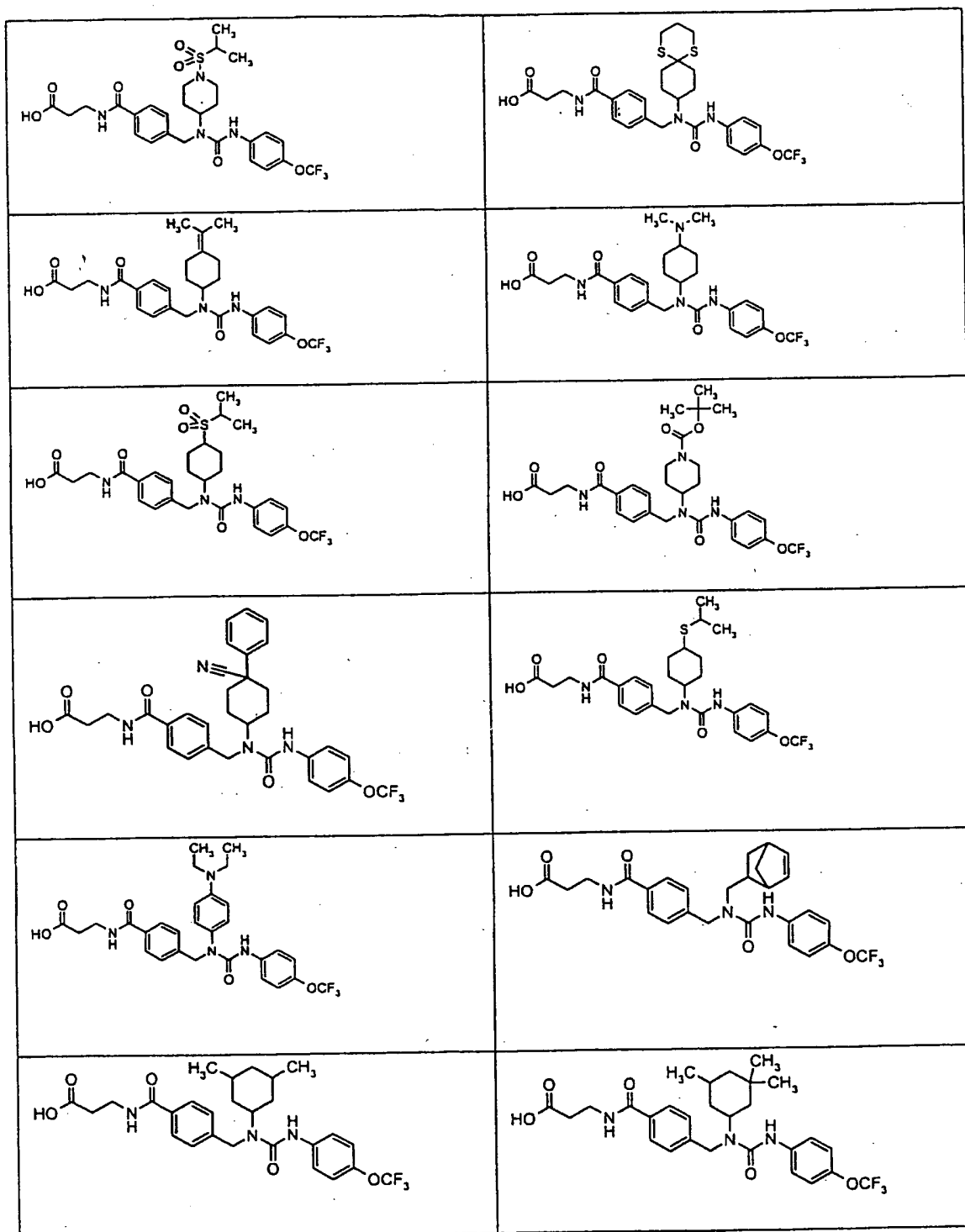


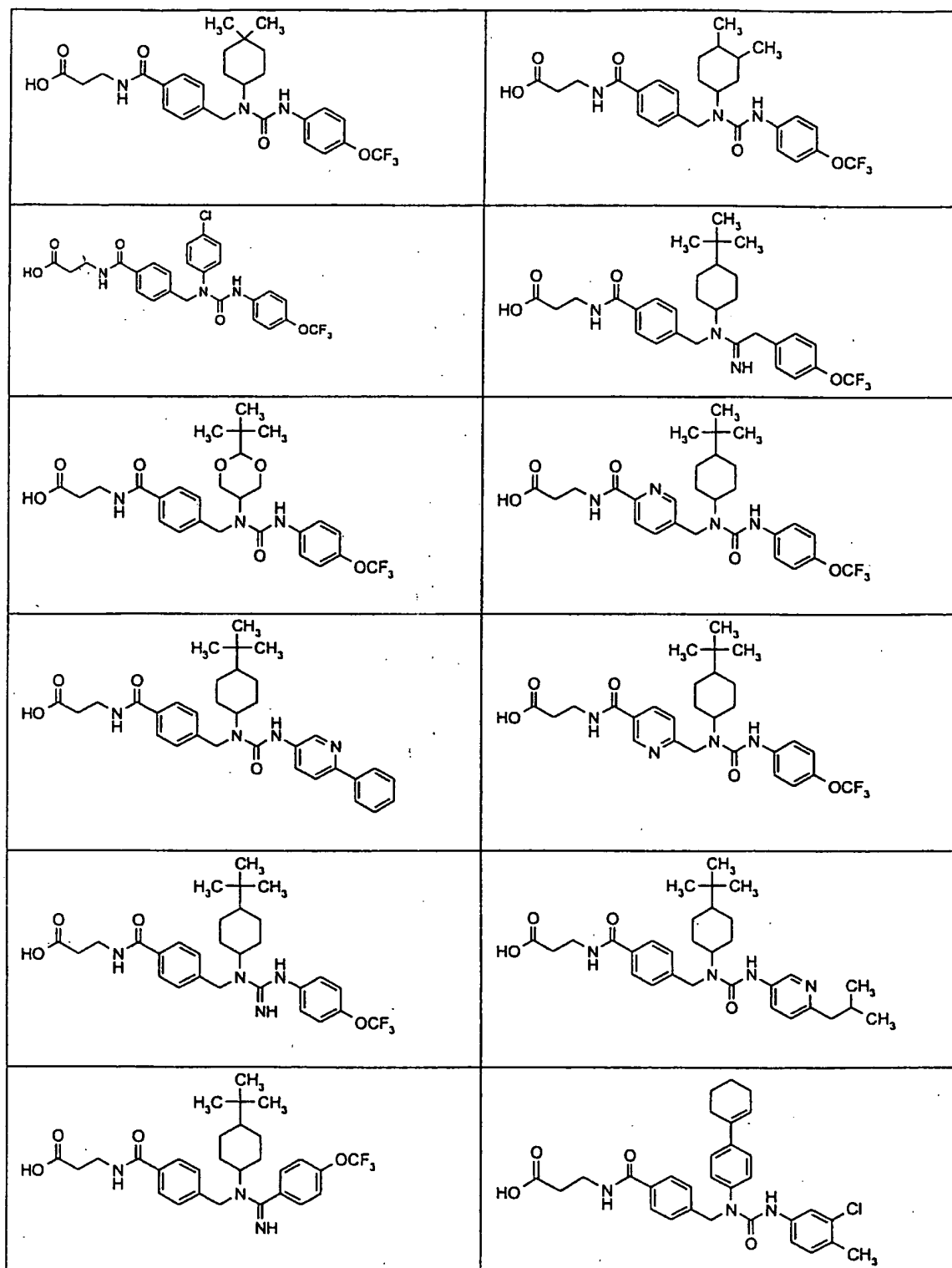
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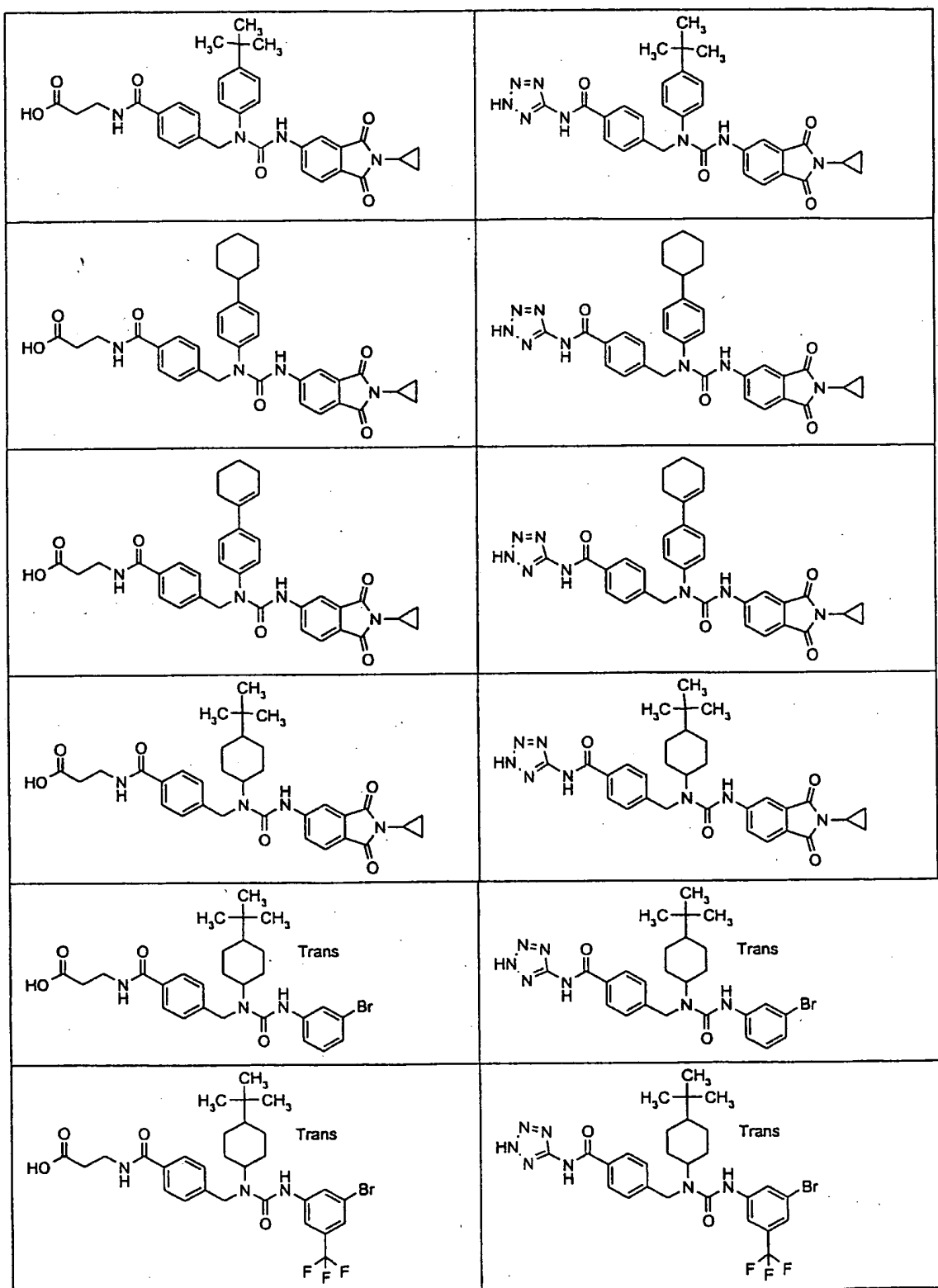


Furthermore, the following preferred compounds according to the invention may be prepared according to the general procedures set forth in the foregoing description:



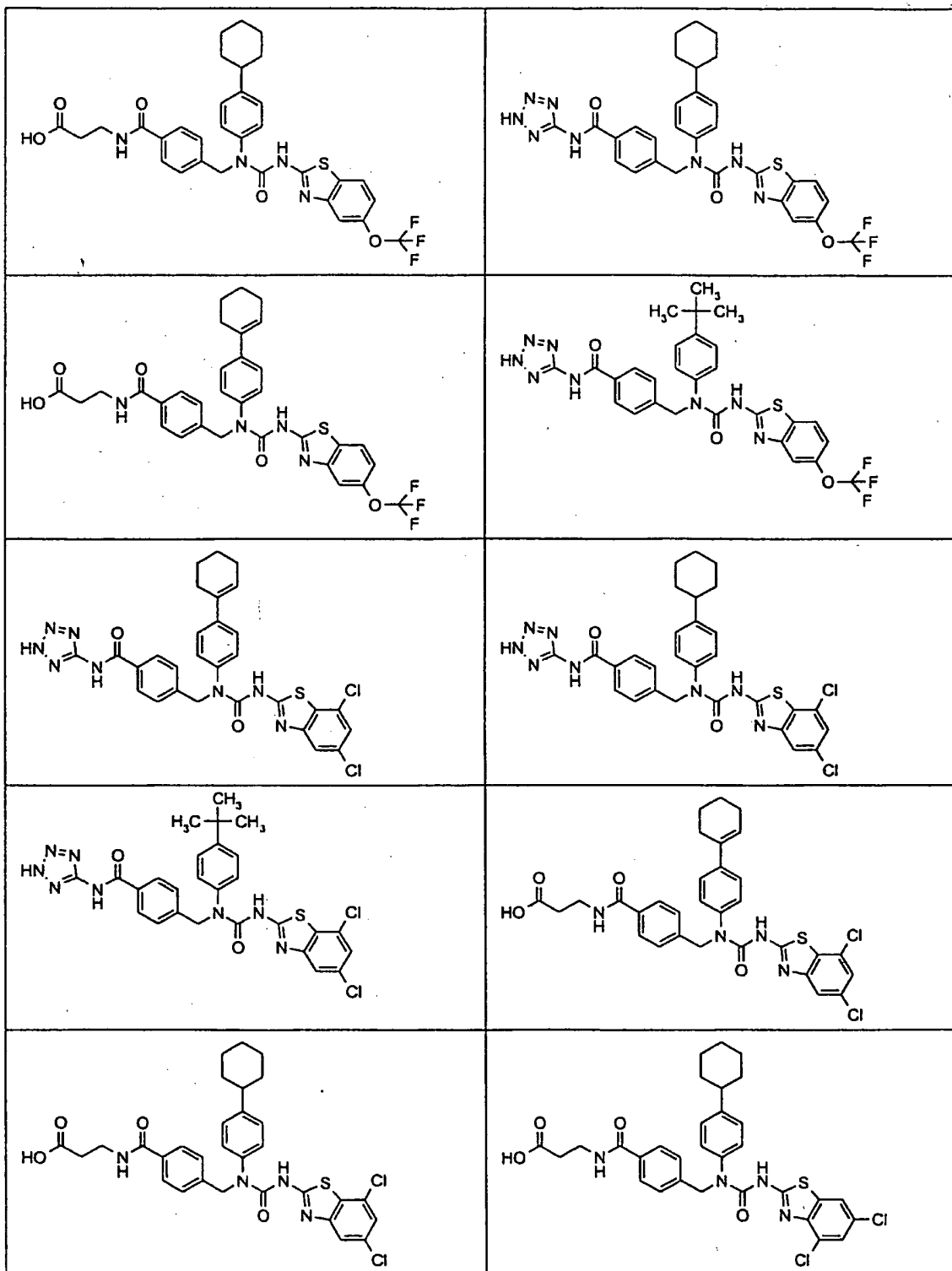


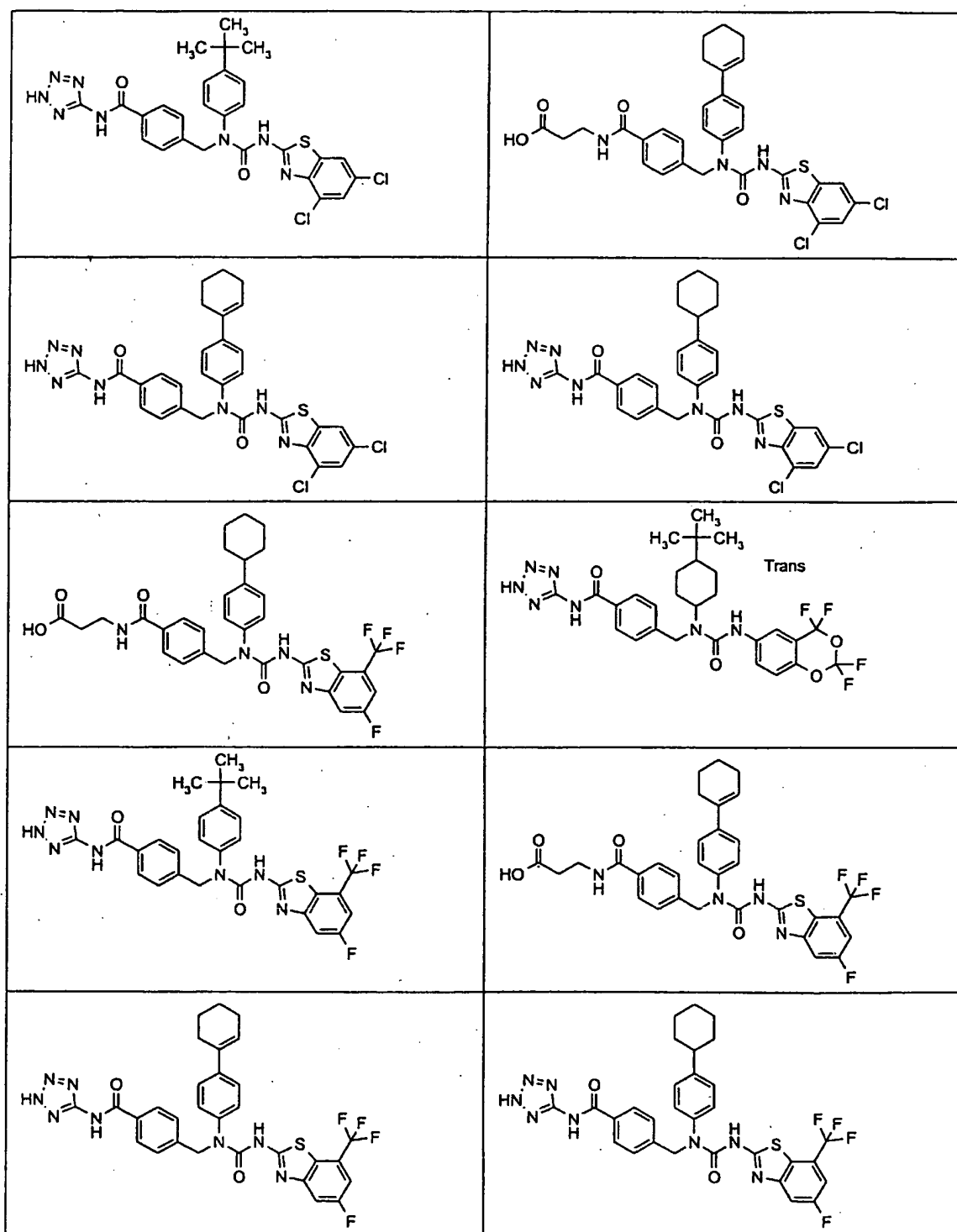


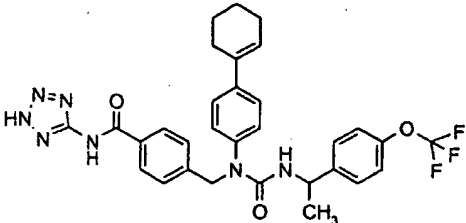
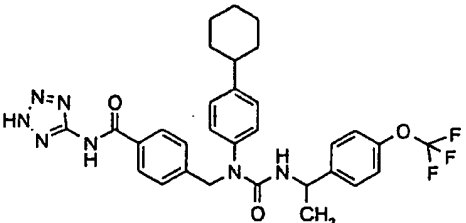
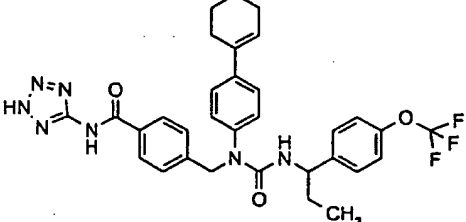
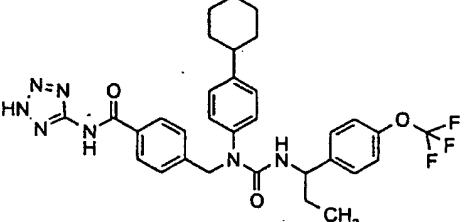
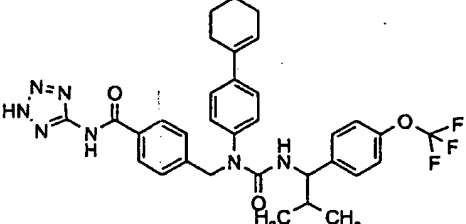
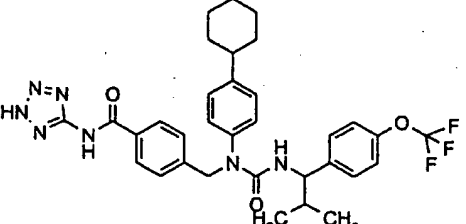
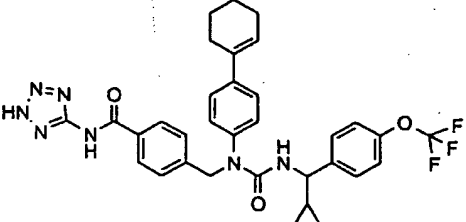
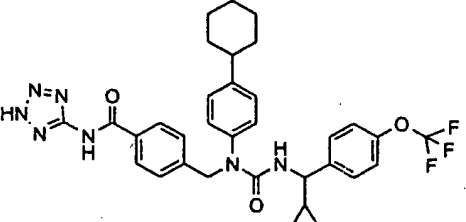
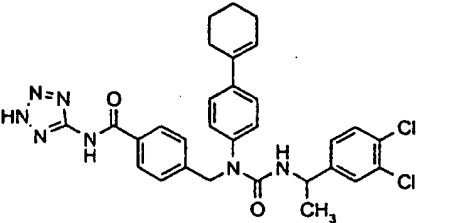
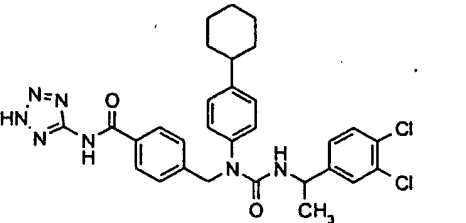


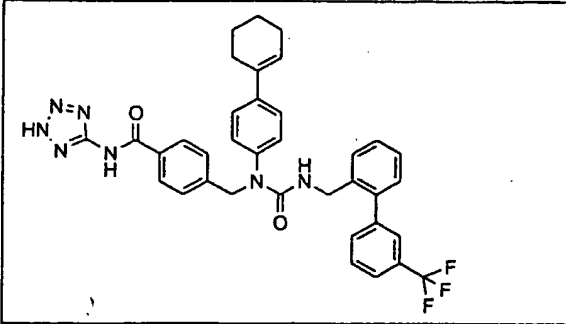
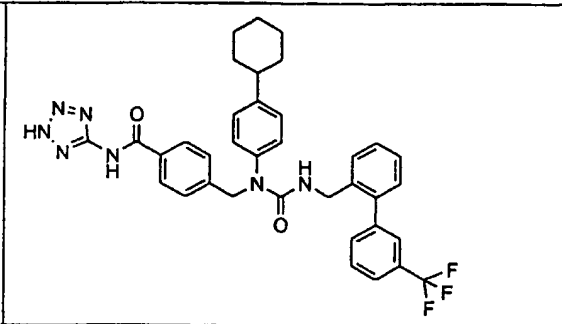
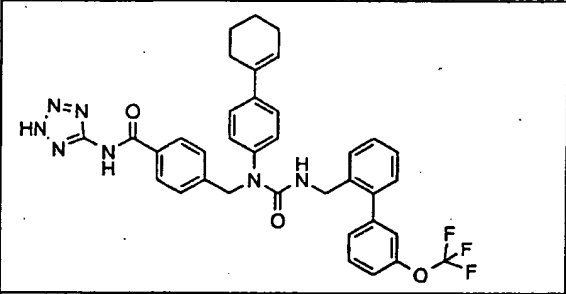
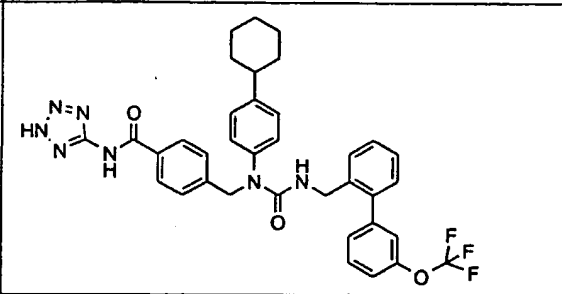
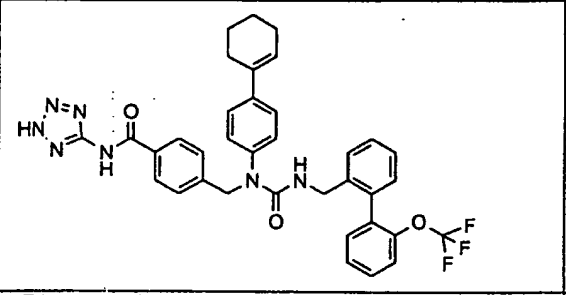
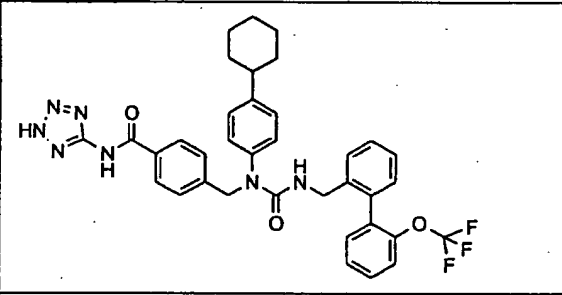
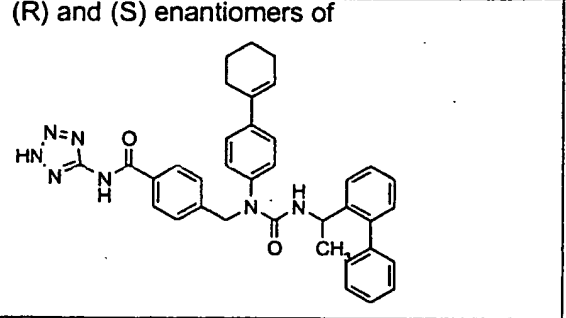
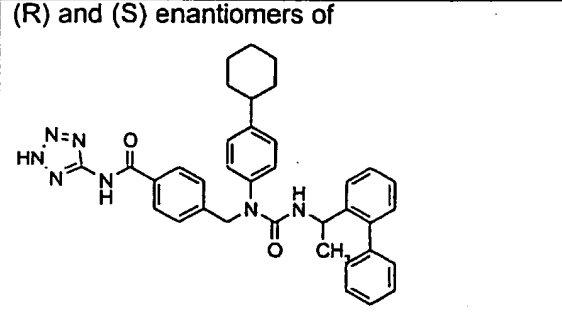
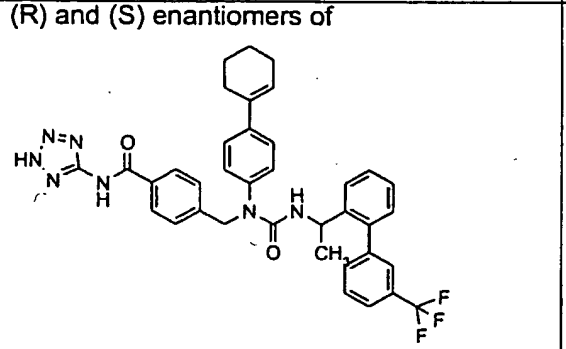
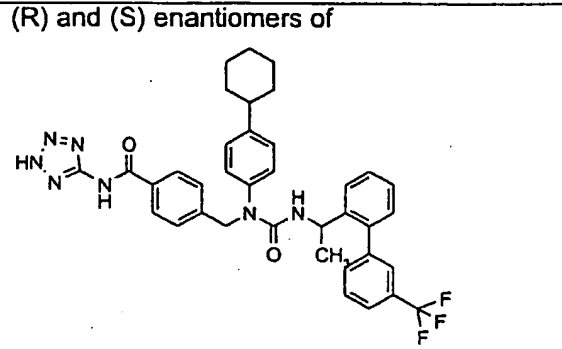


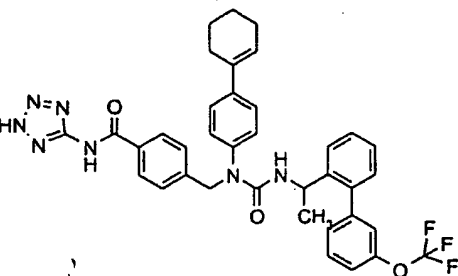
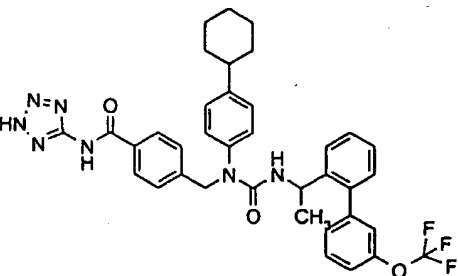
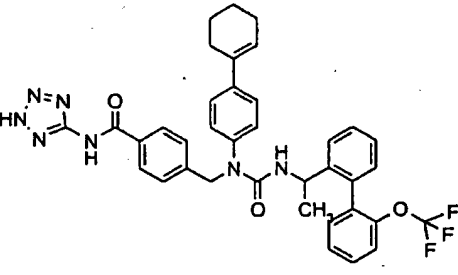
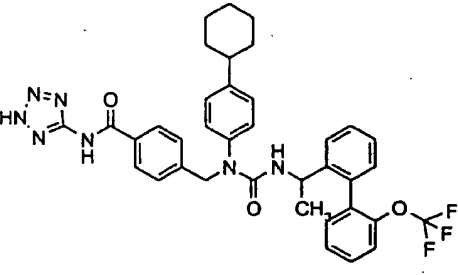
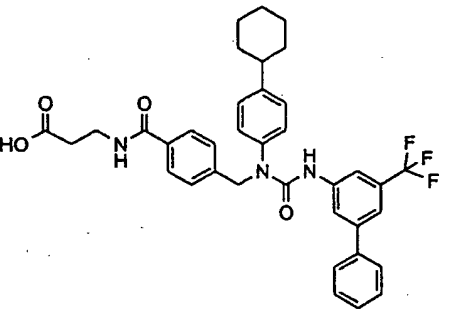
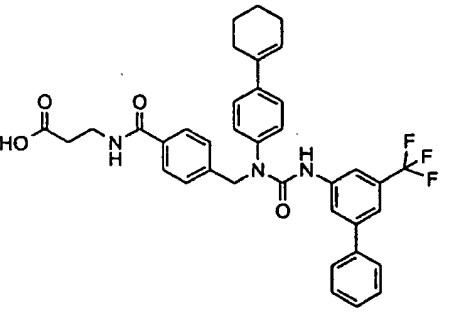
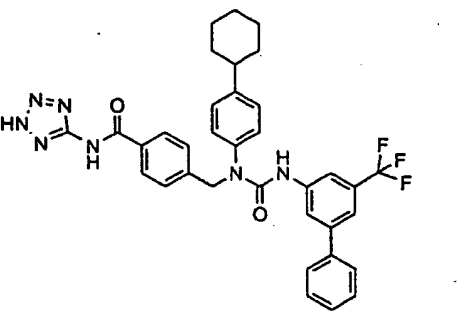
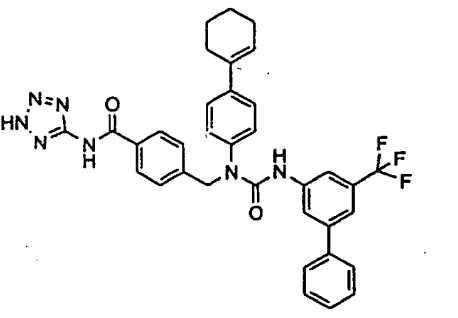
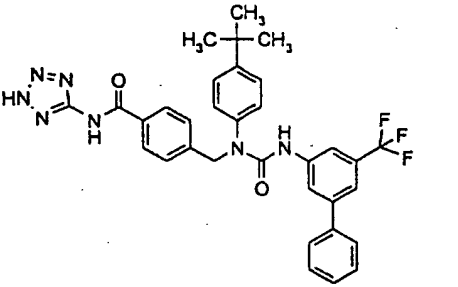
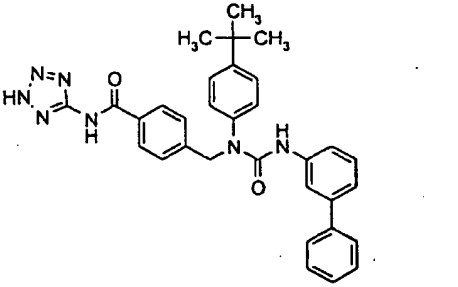


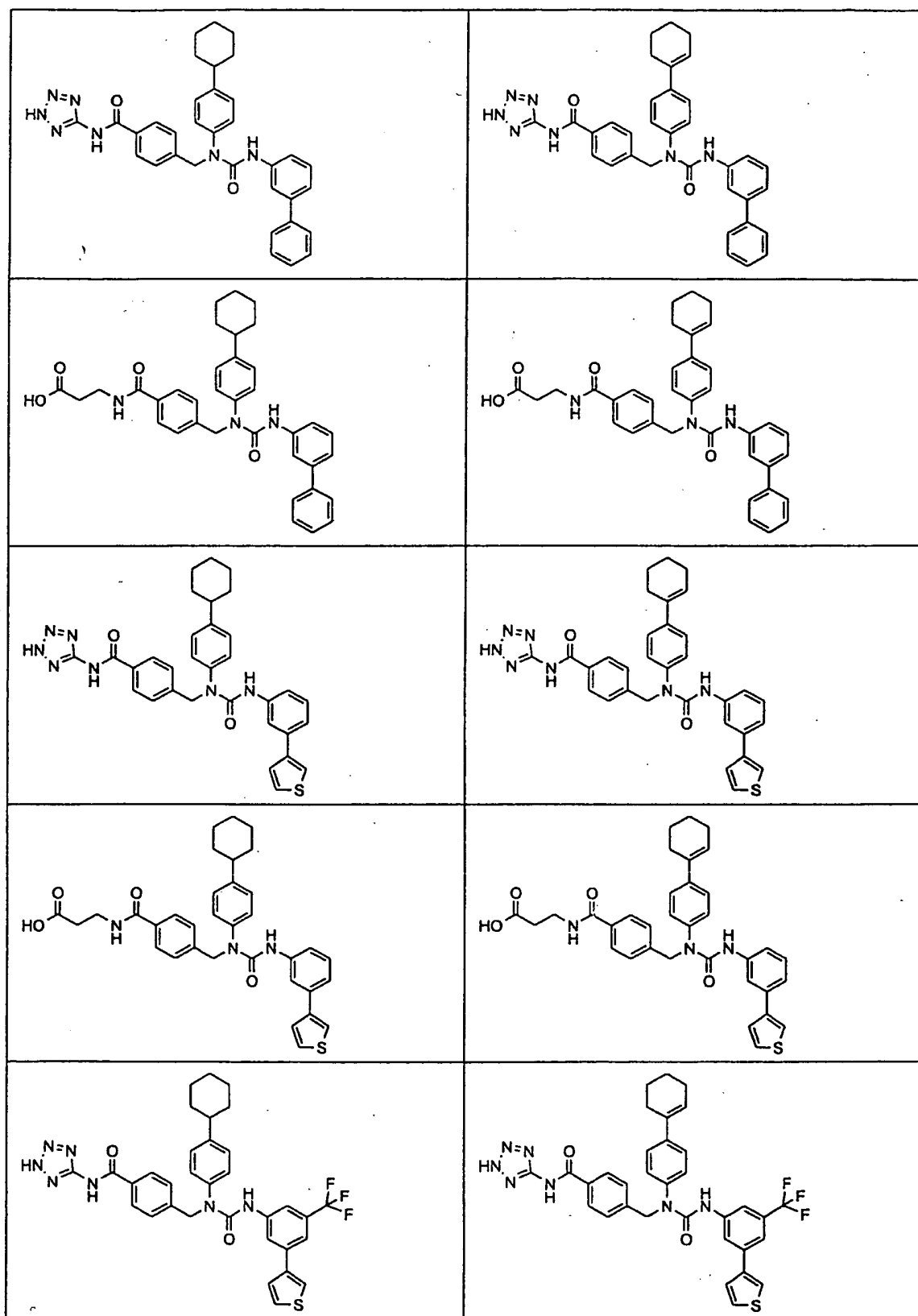


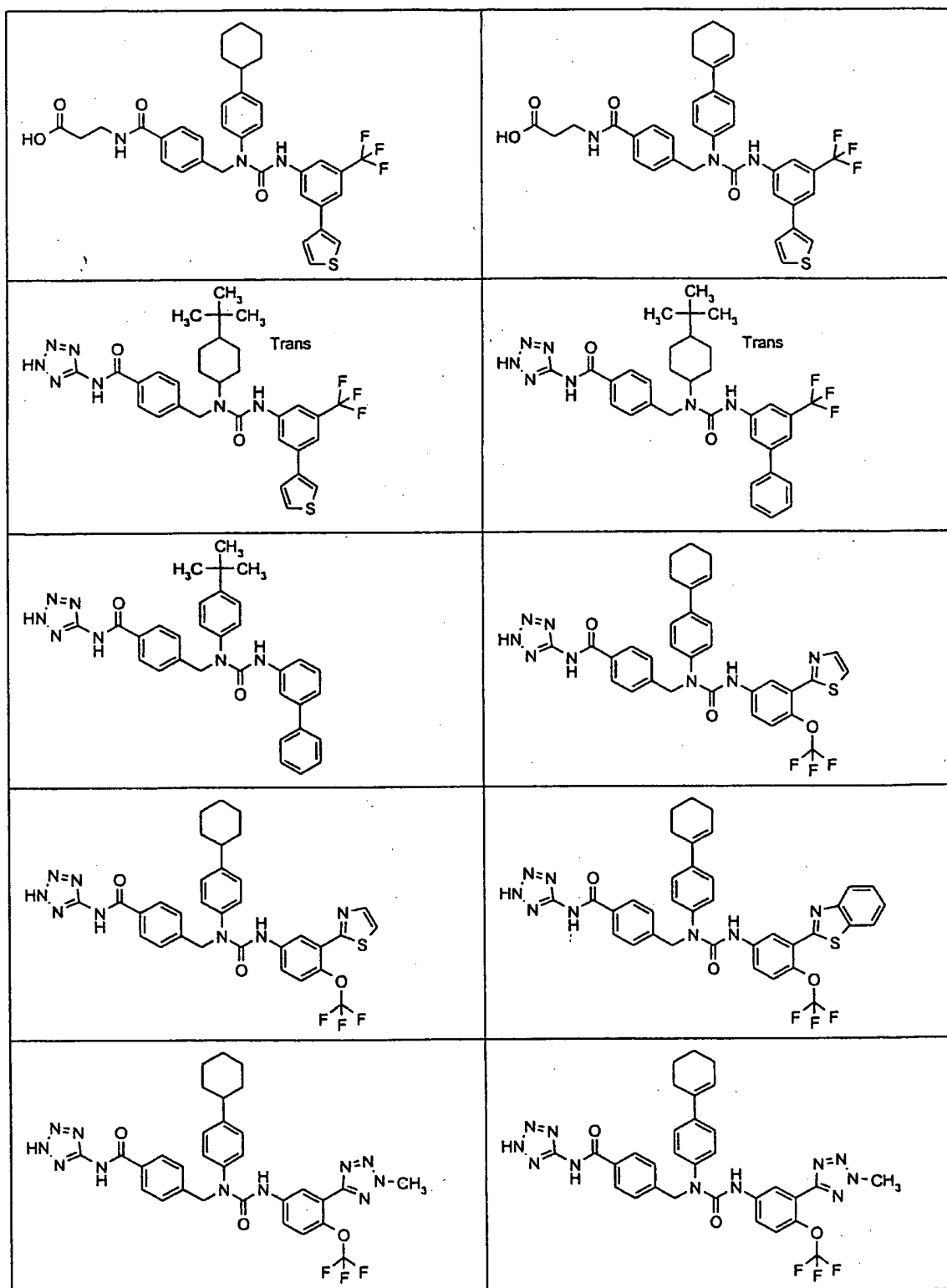


<p>(R) and (S) enantiomers of</p>  <chem>Cc1ccc(OC(F)(F)F)cc1NC(=O)Nc2ccc(cc2C3=CC=C(C=C3)C4=CC=CC=C4C5=CC=CC=C5)C(=O)Nc6nn[nH]n6</chem>	<p>(R) and (S) enantiomers of</p>  <chem>Cc1ccc(OC(F)(F)F)cc1NC(=O)Nc2ccc(cc2C3=CC=C(C=C3)C4=CC=CC=C4C5=CC=CC=C5)C(=O)Nc6nn[nH]n6</chem>
<p>(R) and (S) enantiomers of</p>  <chem>CCc1ccc(OC(F)(F)F)cc1NC(=O)Nc2ccc(cc2C3=CC=C(C=C3)C4=CC=CC=C4C5=CC=CC=C5)C(=O)Nc6nn[nH]n6</chem>	<p>(R) and (S) enantiomers of</p>  <chem>CCc1ccc(OC(F)(F)F)cc1NC(=O)Nc2ccc(cc2C3=CC=C(C=C3)C4=CC=CC=C4C5=CC=CC=C5)C(=O)Nc6nn[nH]n6</chem>
<p>(R) and (S) enantiomers of</p>  <chem>CC(C)C1=CC=C(OC(F)(F)F)C=C1NC(=O)Nc2ccc(cc2C3=CC=C(C=C3)C4=CC=CC=C4C5=CC=CC=C5)C(=O)Nc6nn[nH]n6</chem>	<p>(R) and (S) enantiomers of</p>  <chem>CC(C)C1=CC=C(OC(F)(F)F)C=C1NC(=O)Nc2ccc(cc2C3=CC=C(C=C3)C4=CC=CC=C4C5=CC=CC=C5)C(=O)Nc6nn[nH]n6</chem>
<p>(R) and (S) enantiomers of</p>  <chem>C1CC1C1=CC=C(OC(F)(F)F)C=C1NC(=O)Nc2ccc(cc2C3=CC=C(C=C3)C4=CC=CC=C4C5=CC=CC=C5)C(=O)Nc6nn[nH]n6</chem>	<p>(R) and (S) enantiomers of</p>  <chem>C1CC1C1=CC=C(OC(F)(F)F)C=C1NC(=O)Nc2ccc(cc2C3=CC=C(C=C3)C4=CC=CC=C4C5=CC=CC=C5)C(=O)Nc6nn[nH]n6</chem>
<p>(R) and (S) enantiomers of</p>  <chem>Cc1ccc(Cl)c(Cl)c1NC(=O)Nc2ccc(cc2C3=CC=C(C=C3)C4=CC=CC=C4C5=CC=CC=C5)C(=O)Nc6nn[nH]n6</chem>	<p>(R) and (S) enantiomers of</p>  <chem>Cc1ccc(Cl)c(Cl)c1NC(=O)Nc2ccc(cc2C3=CC=C(C=C3)C4=CC=CC=C4C5=CC=CC=C5)C(=O)Nc6nn[nH]n6</chem>

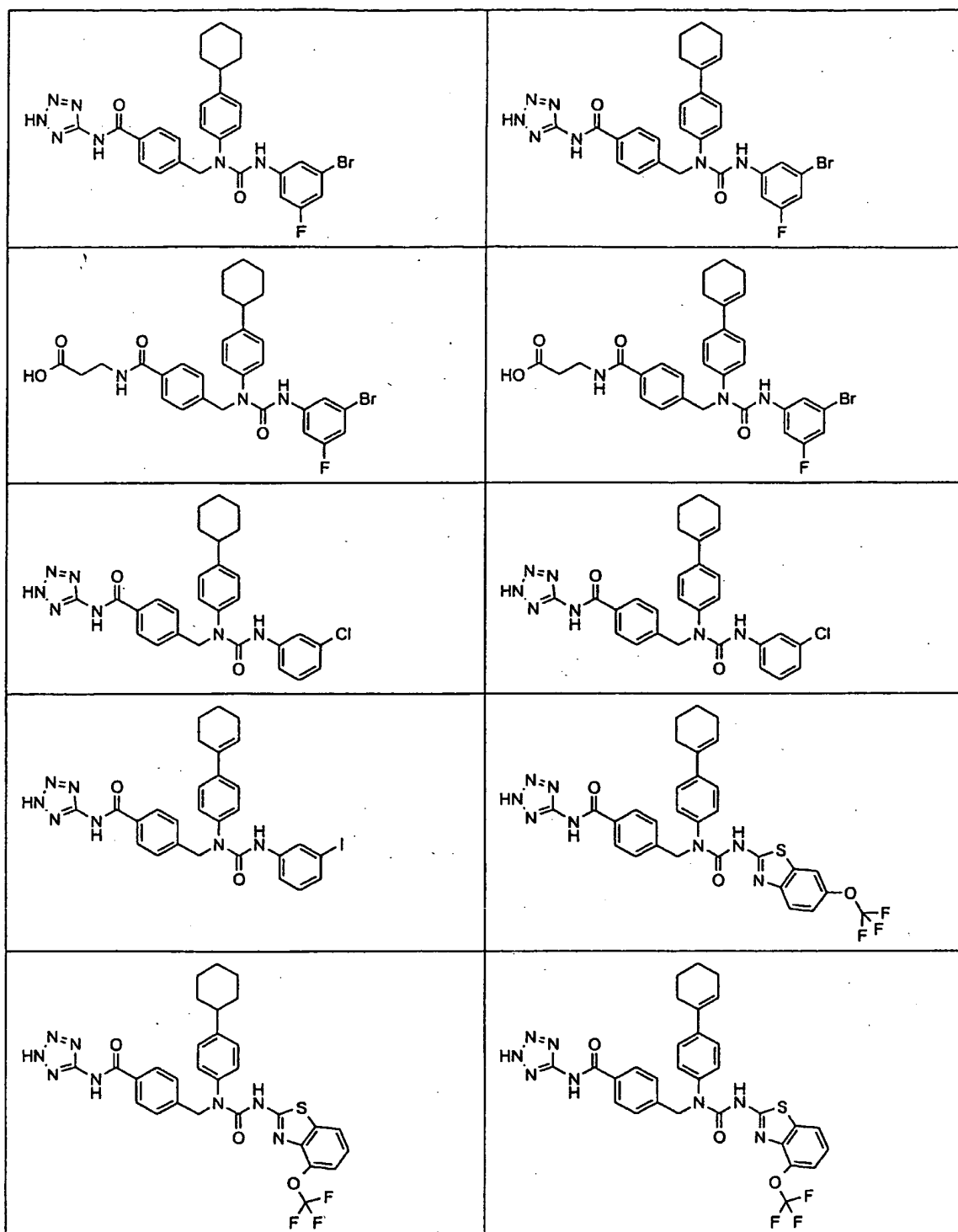
	
	
	
(R) and (S) enantiomers of 	(R) and (S) enantiomers of 
(R) and (S) enantiomers of 	(R) and (S) enantiomers of 

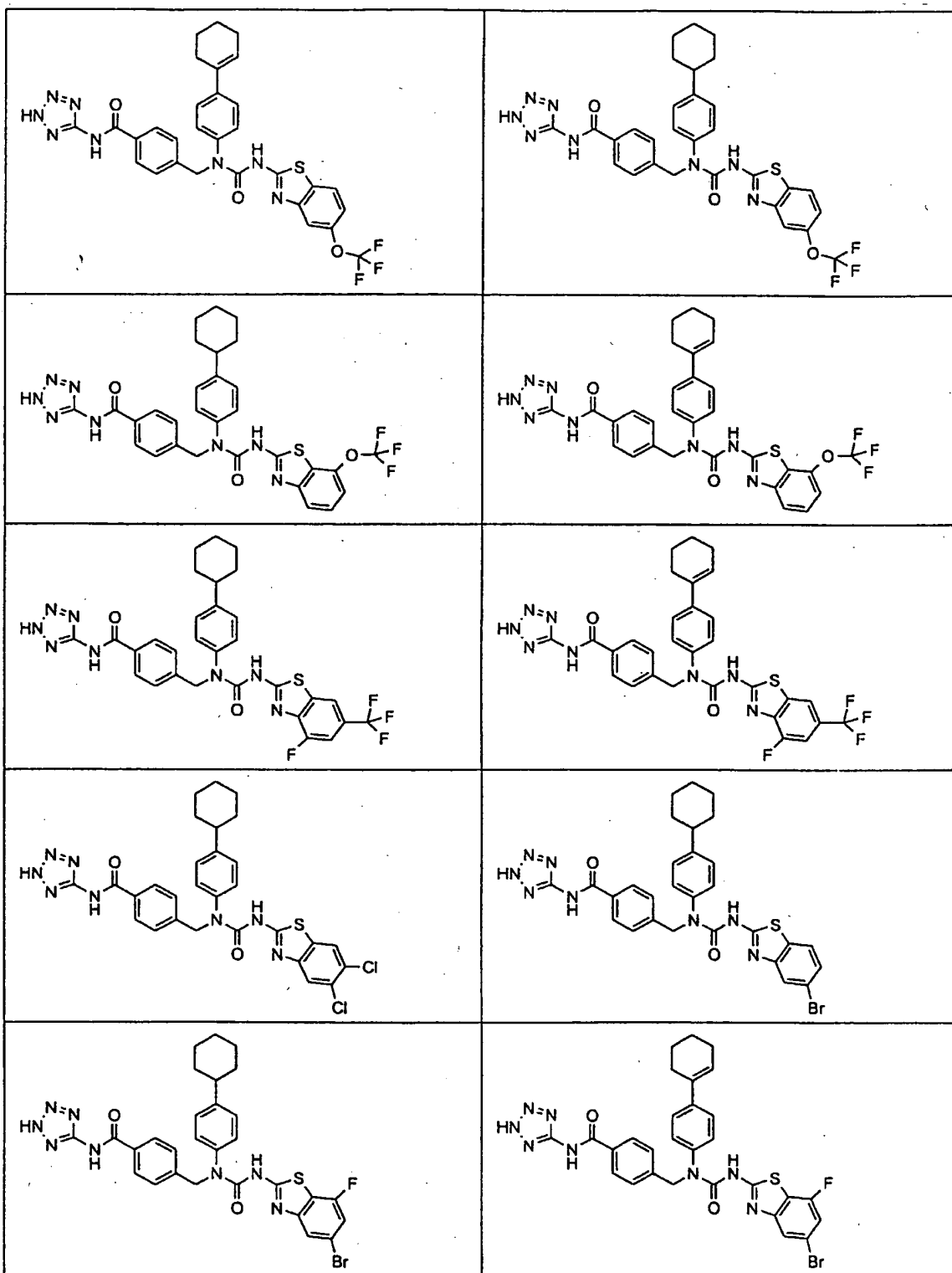
<p>(R) and (S) enantiomers of</p> 	<p>(R) and (S) enantiomers of</p> 
<p>(R) and (S) enantiomers of</p> 	<p>(R) and (S) enantiomers of</p> 
	
	
	

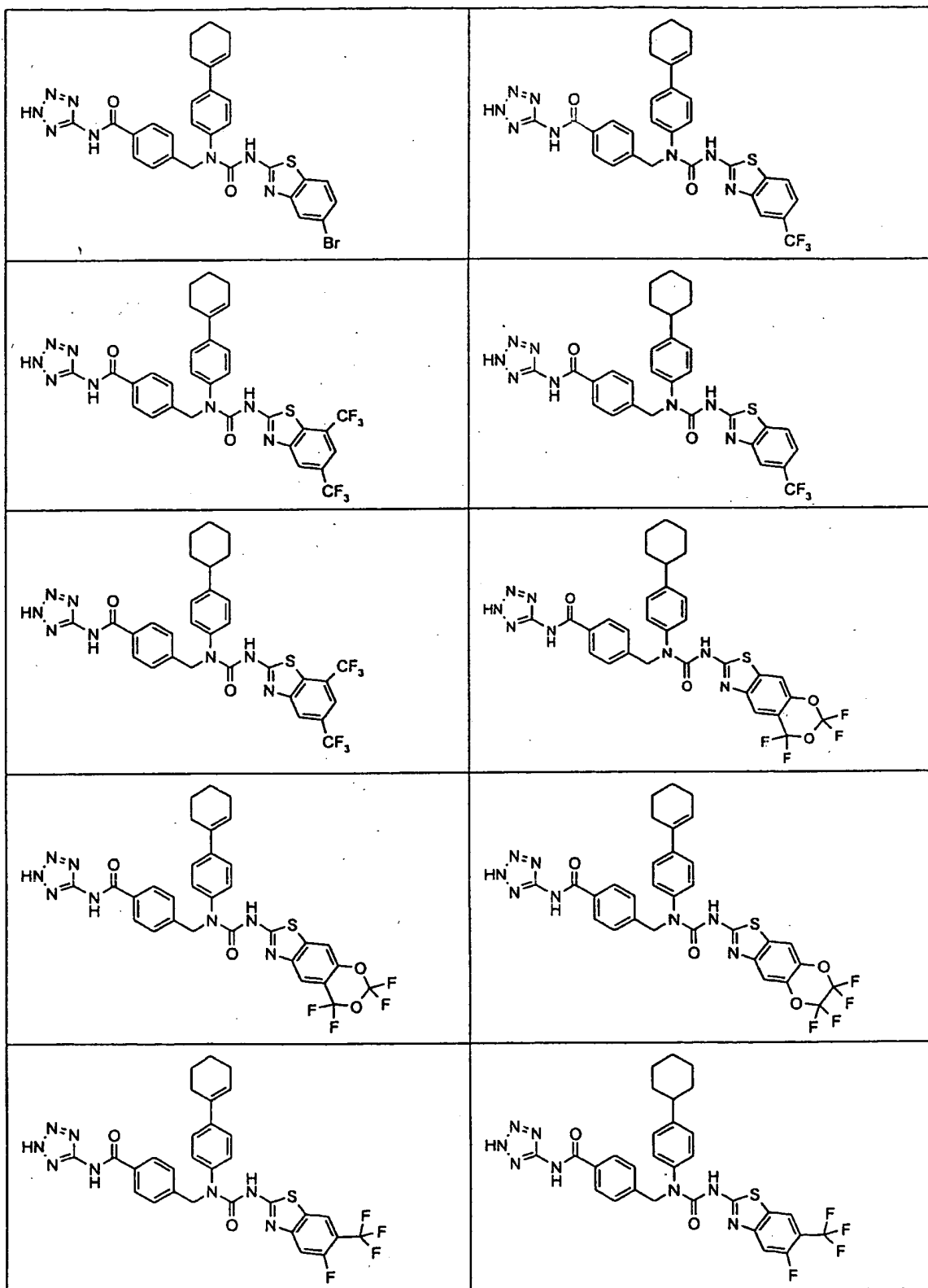


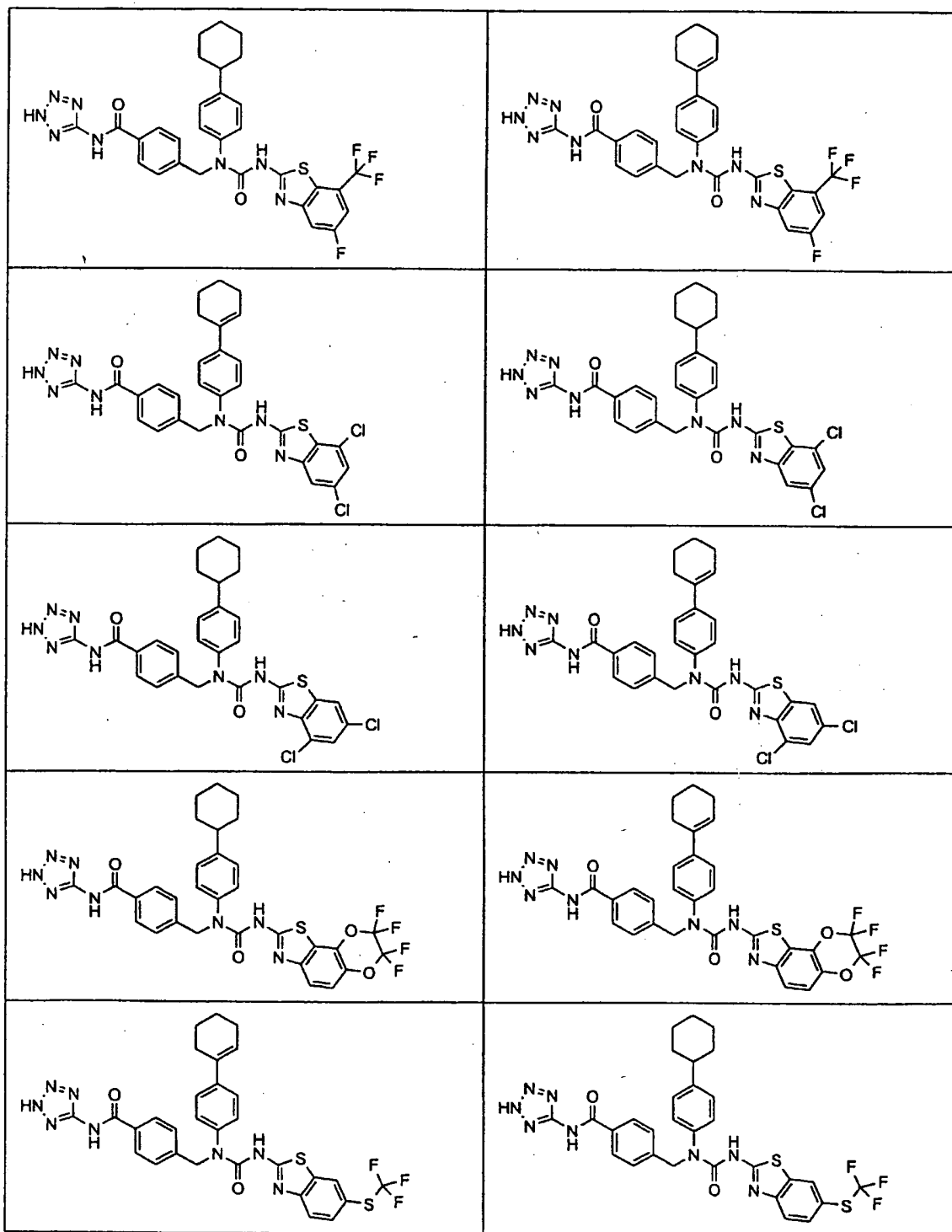


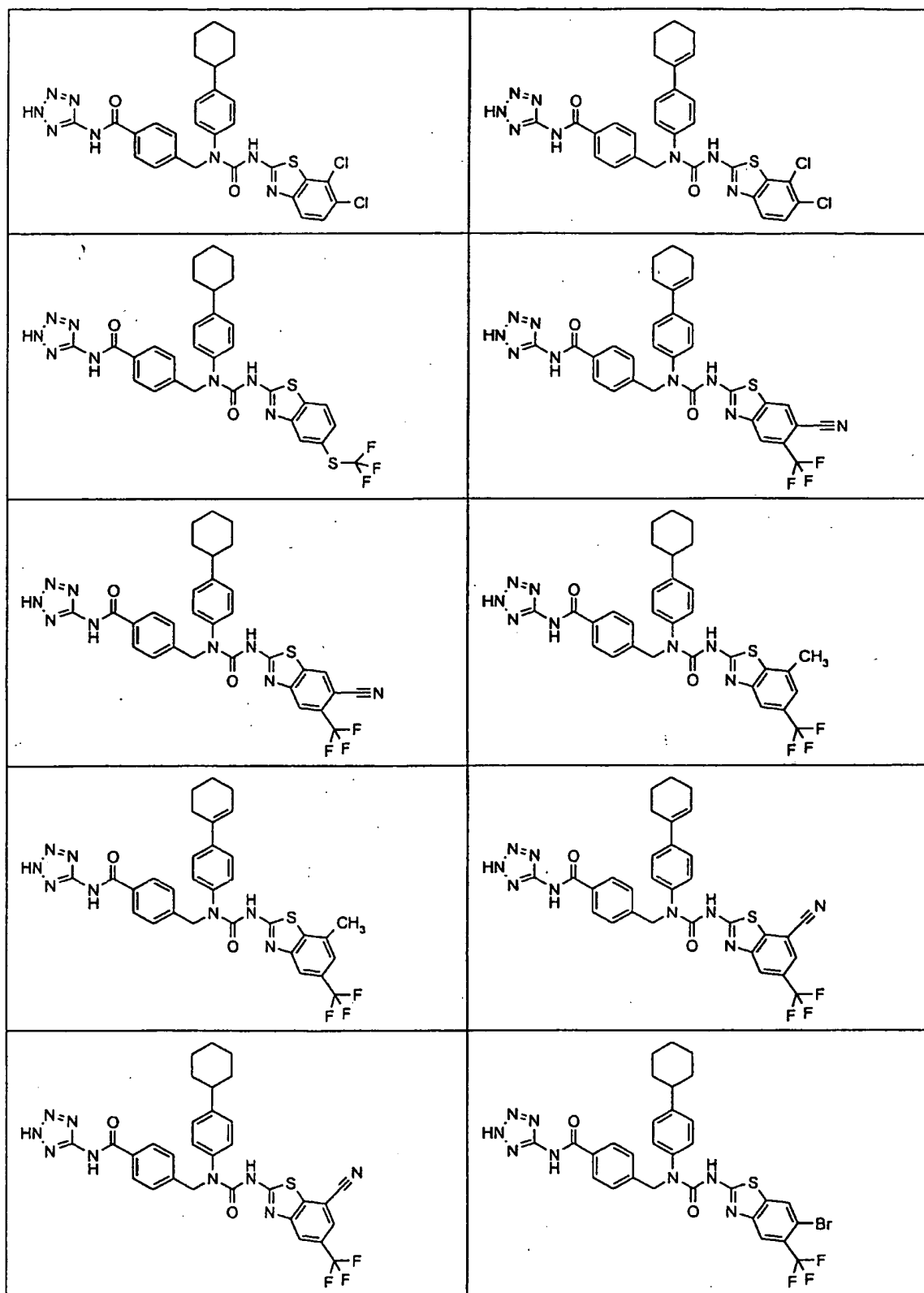






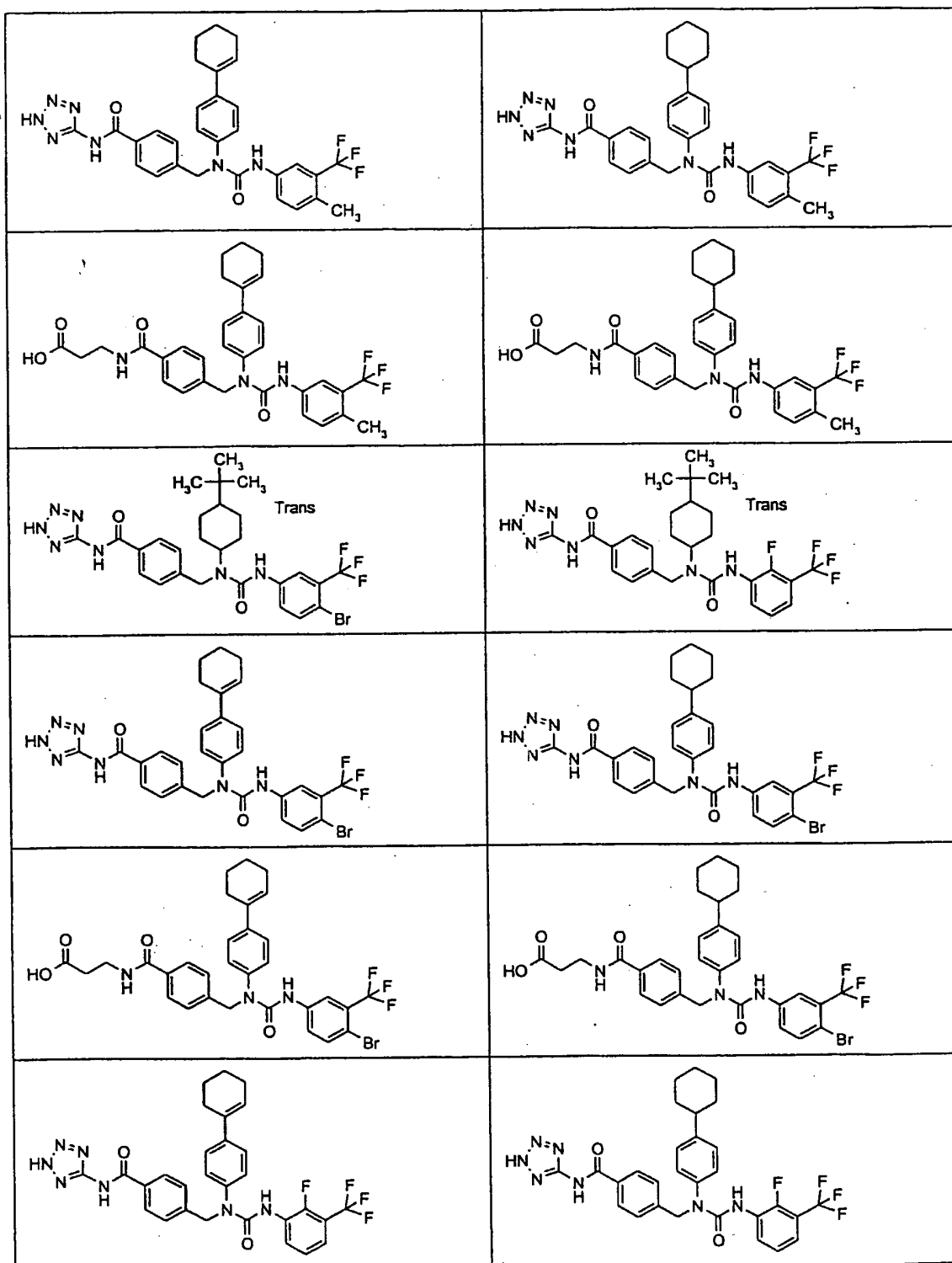






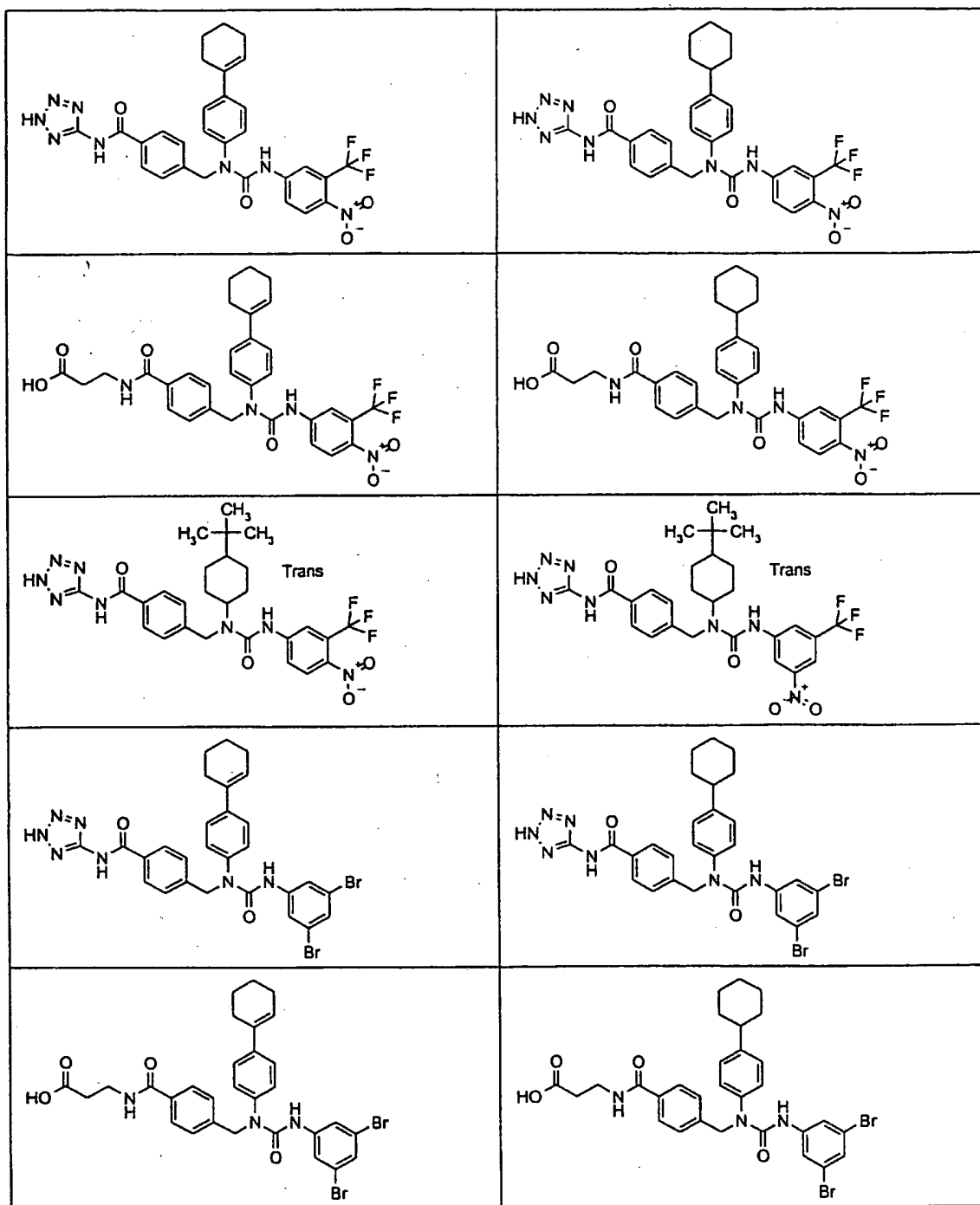


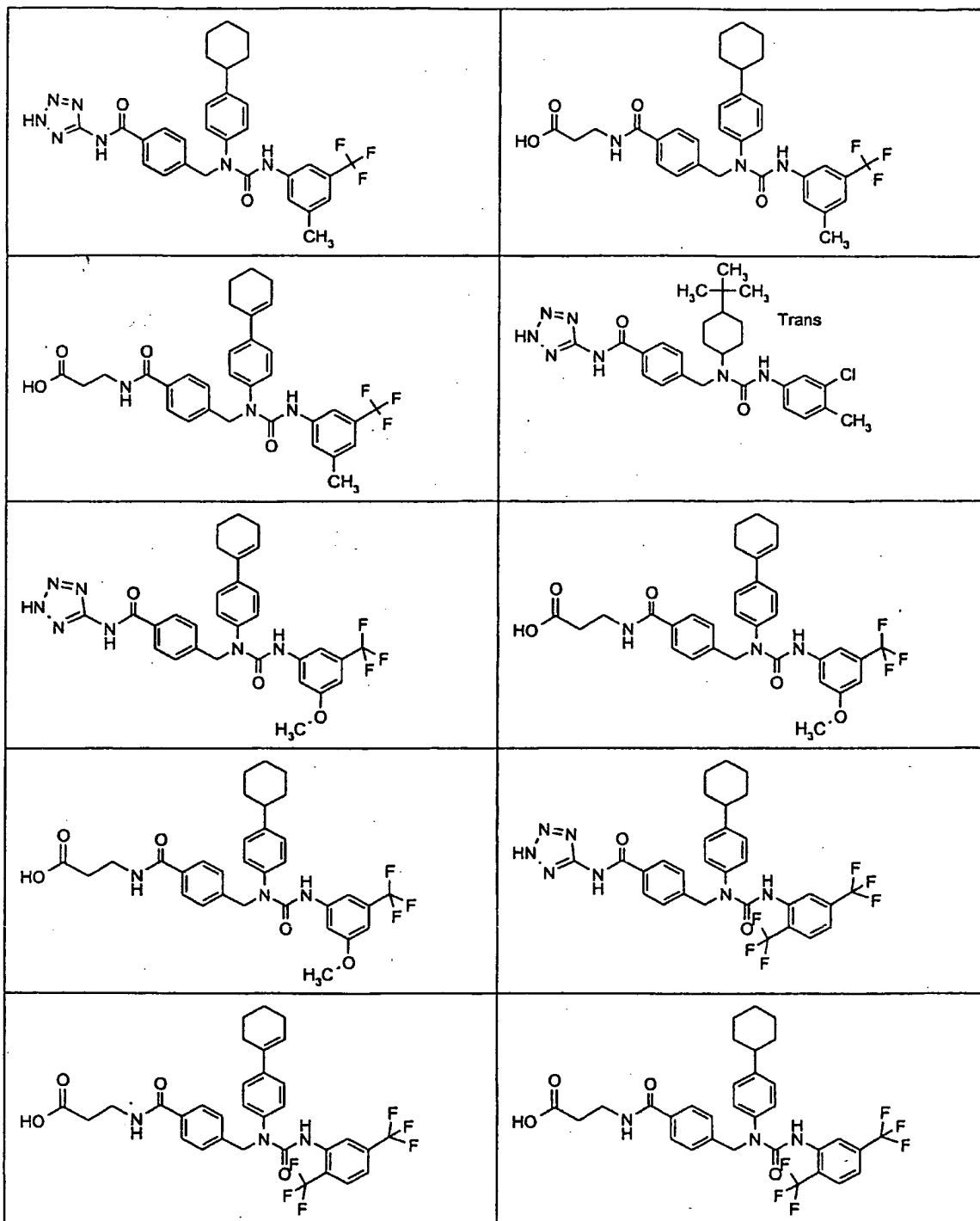




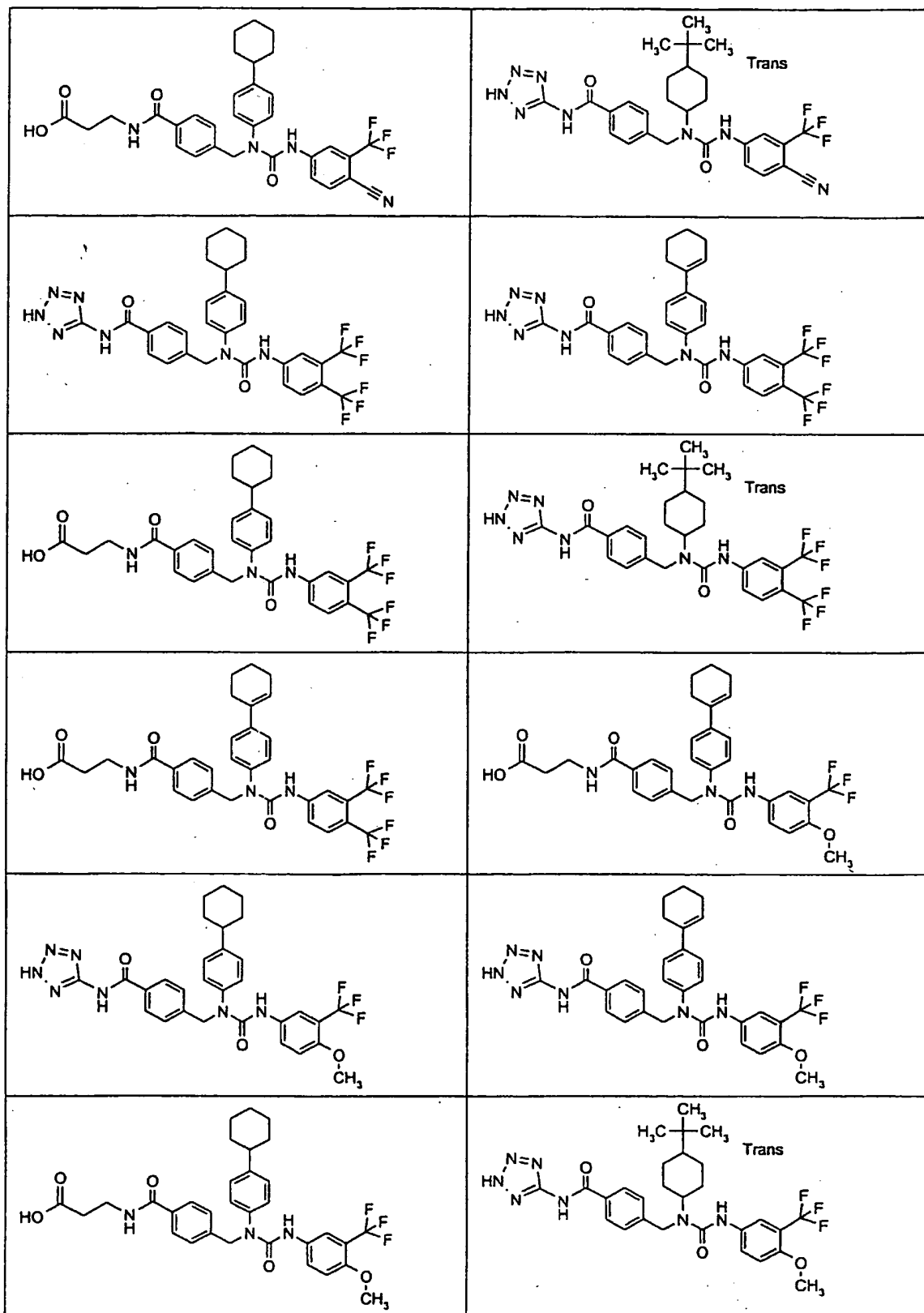


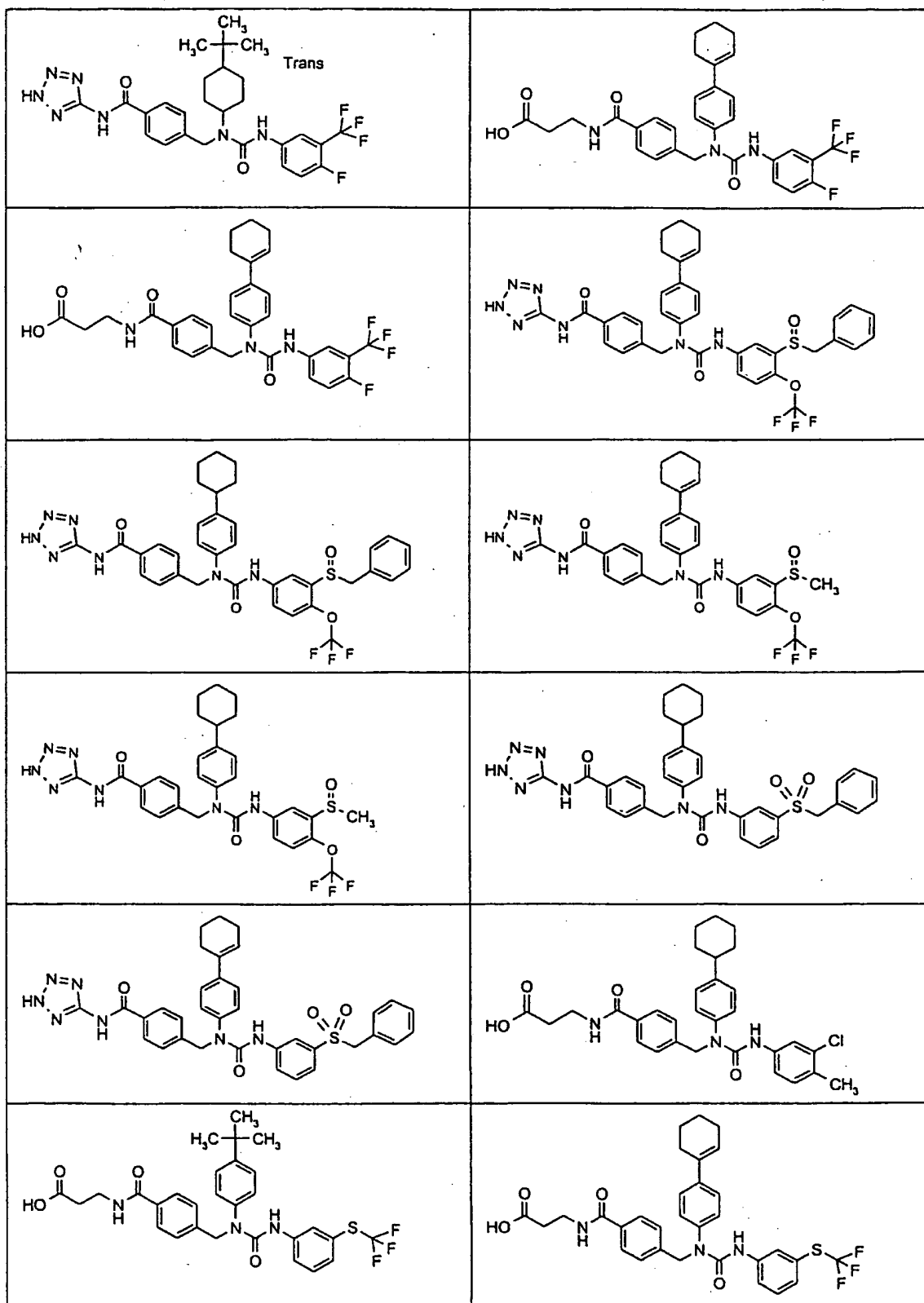


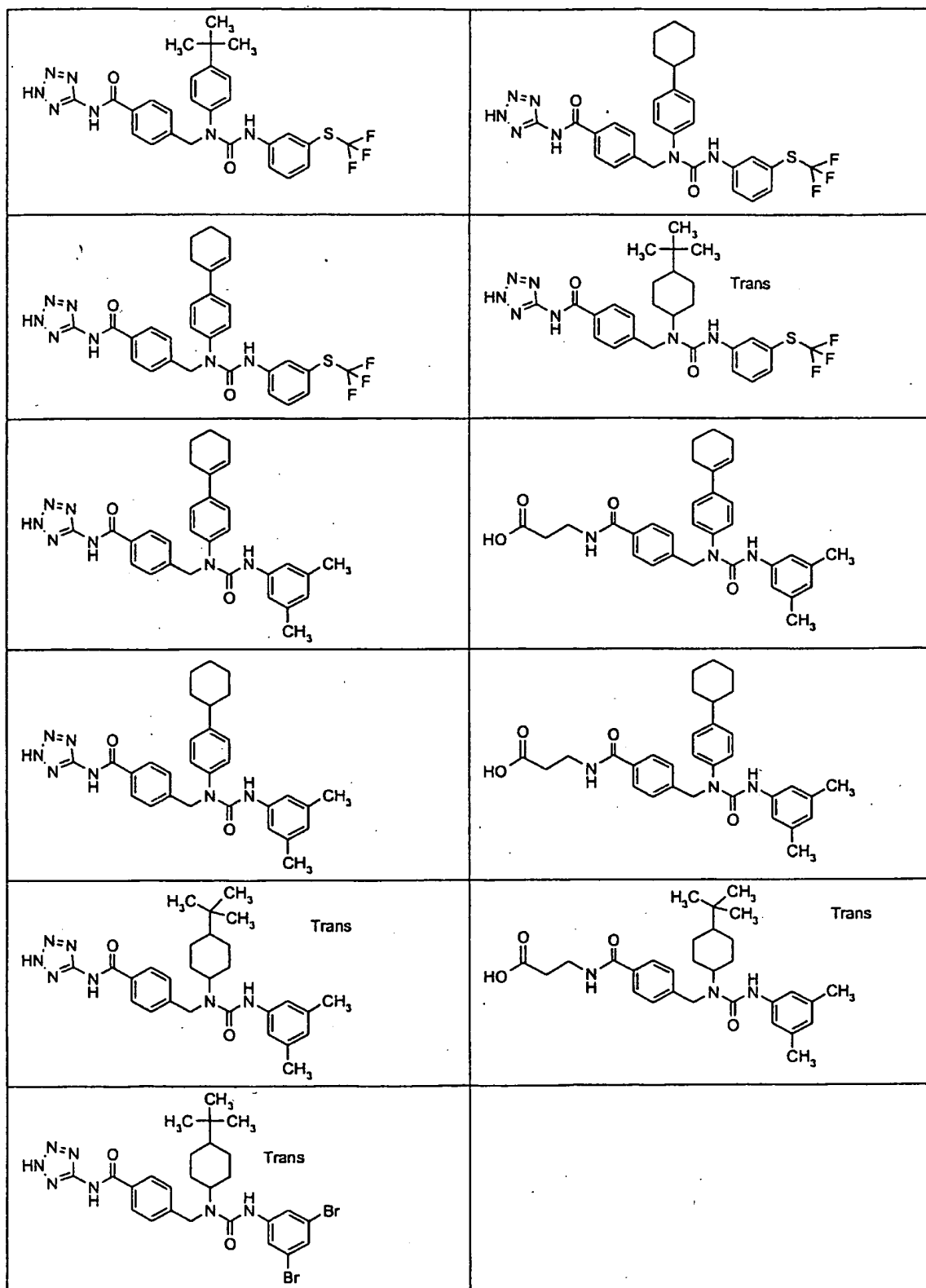












It should be apparent from the foregoing that other starting materials and other intermediate compounds can be substituted in the above procedures to prepare all of the compounds of the invention. The methods disclosed herein are based on established chemical techniques, as will be apparent to those skilled in the art, and therefore all of the compounds of the invention are

5 broadly enabled by the preceding disclosure.

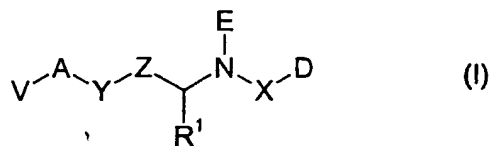
Accordingly, the invention may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive, and the scope of the invention is, therefore, indicated by the appending claims rather than by the foregoing description. All modifications, which

10 come within the meaning and range of the lawful equivalency of the claims, are to be embraced within their scope.



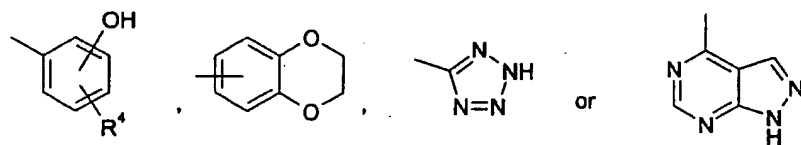
## CLAIMS

1. A compound of the general formula (I):



wherein

V is  $-\text{C}(\text{O})\text{OR}^2$ ,  $-\text{C}(\text{O})\text{NR}^2\text{R}^3$ ,  $-\text{C}(\text{O})\text{NR}^2\text{OR}^3$ ,  $-\text{S}(\text{O})_2\text{OR}^2$ ,



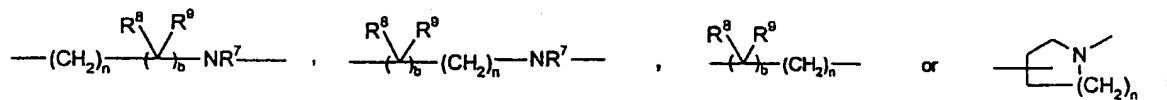
wherein

$\text{R}^2$  and  $\text{R}^3$  independently are hydrogen or  $\text{C}_{1-8}$ -alkyl,

$\text{R}^4$  is hydrogen, halogen,  $-\text{CN}$ ,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ ,  $-\text{NO}_2$ ,  $-\text{OR}^5$ ,  $-\text{NR}^5\text{R}^6$  or  $\text{C}_{1-8}$ -alkyl,

wherein  $\text{R}^5$  and  $\text{R}^6$  independently are hydrogen or  $\text{C}_{1-8}$ -alkyl,

A is



wherein

b is 0 or 1,

n is 0, 1, 2 or 3,

$R^7$  is hydrogen,  $C_{1-6}$ -alkyl or  $C_{3-8}$ -cycloalkyl- $C_{1-6}$ -alkyl,

$R^8$  and  $R^9$  independently are hydrogen or  $C_{1-6}$ -alkyl,

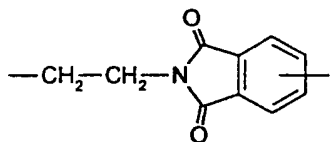
5 Y is  $-C(O)-$ ,  $-S(O)_2-$ ,  $-O-$  or a valence bond,

Z is phenylene or a divalent radical derived from a 5 or 6 membered heteroaromatic ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur,

10 which may optionally be substituted with one or two groups  $R^{46}$  and  $R^{47}$  selected from hydrogen, halogen,  $-CN$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-NO_2$ ,  $-OR^{10}$ ,  $-NR^{10}R^{11}$  and  $C_{1-6}$ -alkyl,

wherein  $R^{10}$  and  $R^{11}$  independently are hydrogen or  $C_{1-6}$ -alkyl,

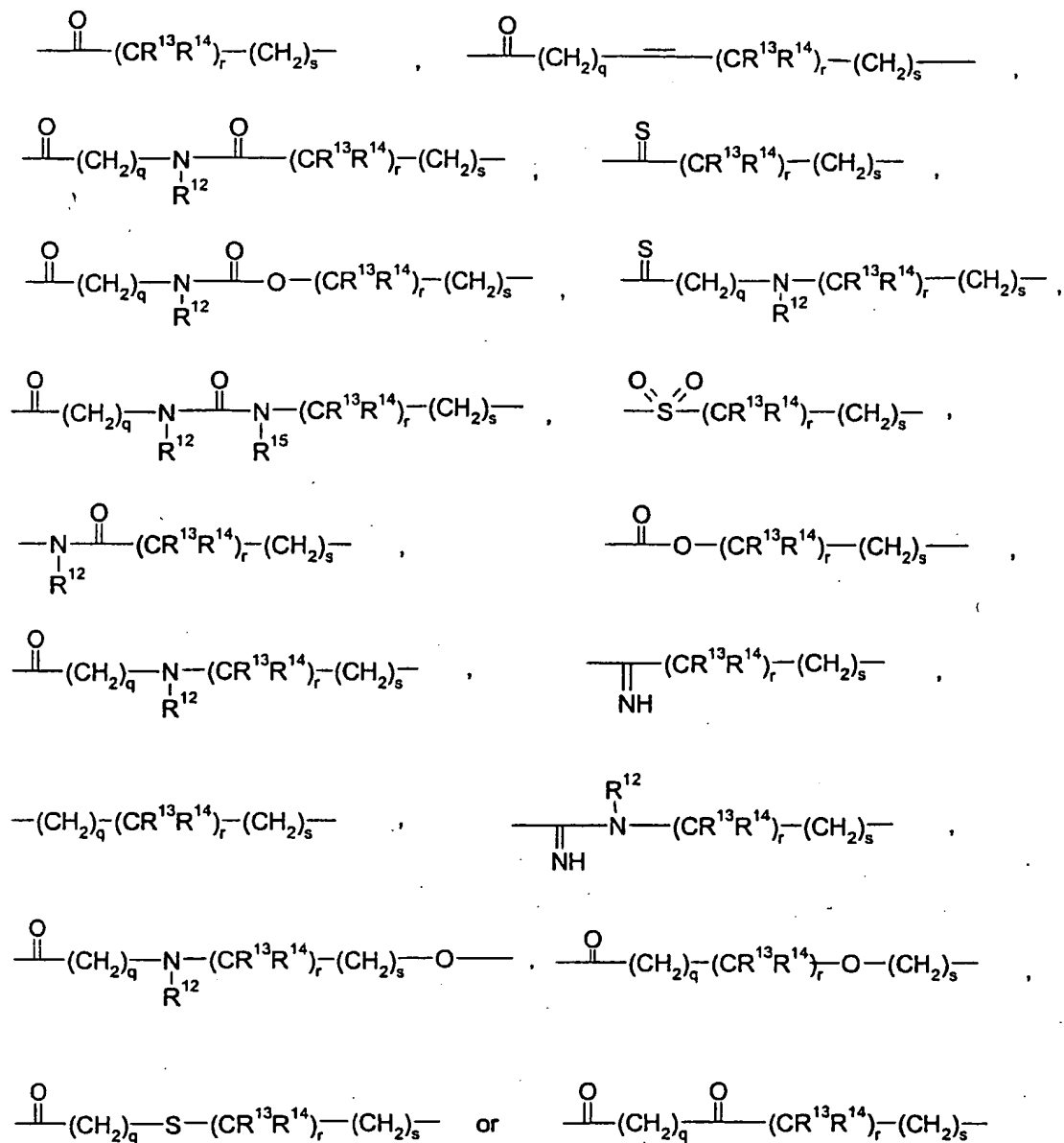
or -A-Y-Z- together are



15

$R^1$  is hydrogen or  $C_{1-6}$ -alkyl,

X is



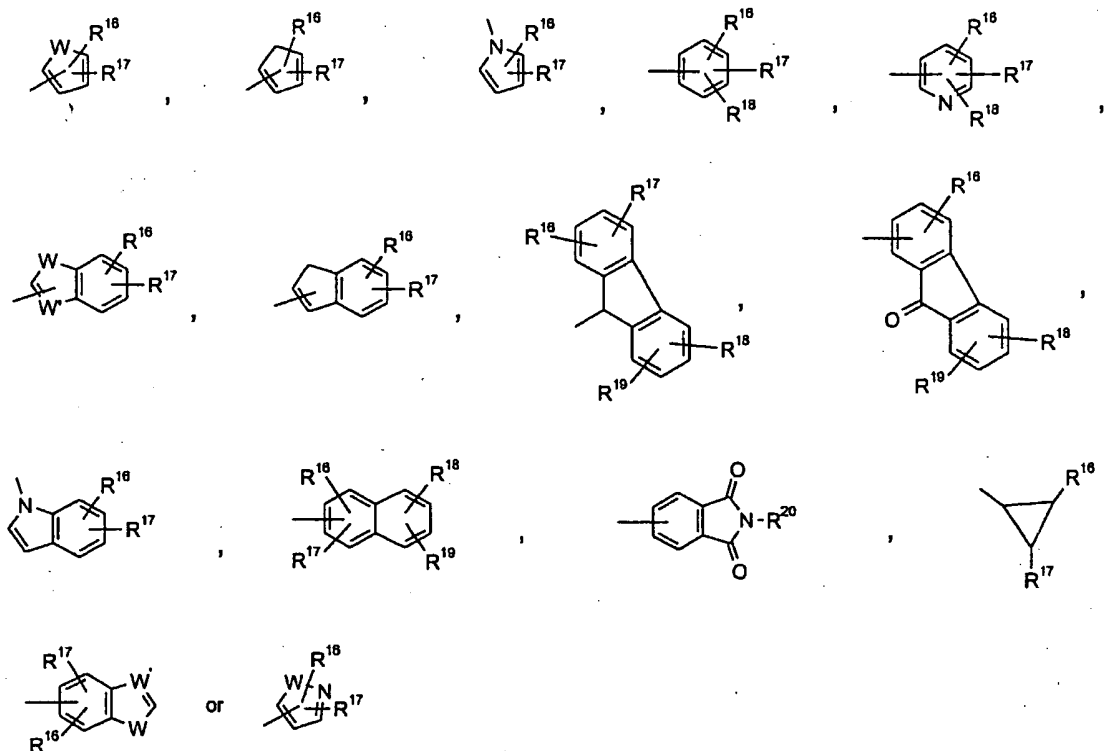
5 wherein

r is 0 or 1,

q and s independently are 0, 1, 2 or 3,

$R^{12}$ ,  $R^{13}$ ,  $R^{14}$  and  $R^{15}$  independently are hydrogen or  $C_{1-6}$ -alkyl,

D is



5

wherein

W is -O-, -S-, -S(O)<sub>2</sub>- or -NR<sup>20</sup>-,

10

W' is =CR<sup>20'</sup>- or =N-,

$R^{16}$ ,  $R^{17}$ ,  $R^{18}$  and  $R^{19}$  independently are

- 15
- hydrogen, halogen, -CN, -CH<sub>2</sub>CN, -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -OS(O)<sub>2</sub>CF<sub>3</sub>, -SCF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>, -SR<sup>21</sup>, -NR<sup>21</sup>S(O)<sub>2</sub>R<sup>22</sup>, -S(O)<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>, -S(O)NR<sup>21</sup>R<sup>22</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -OS(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, -OC(O)NR<sup>21</sup>R<sup>22</sup>, -NR<sup>21</sup>C(O)R<sup>22</sup>, -CH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -CH<sub>2</sub>OR<sup>21</sup>, -CH<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>, -OC(O)R<sup>21</sup>, -C(O)R<sup>21</sup> or -C(O)OR<sup>21</sup>,

20

- C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl or C<sub>2-6</sub>-alkynyl,

which may optionally be substituted with one or more substituents selected from -  
 CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -SCF<sub>3</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>,  
 -SR<sup>21</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, -OC(O)NR<sup>21</sup>R<sup>22</sup>, -NR<sup>21</sup>C(O)R<sup>22</sup>,  
 -OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -C(O)R<sup>21</sup> and -C(O)OR<sup>21</sup>,

- C<sub>3-8</sub>-cycloalkyl, C<sub>4-8</sub>-cycloalkenyl, heterocyclyl, C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkyl, C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkoxy, C<sub>3-8</sub>-cycloalkyloxy, C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkylthio, C<sub>3-8</sub>-cycloalkylthio, C<sub>3-8</sub>-cycloalkyl-C<sub>2-6</sub>-alkenyl, C<sub>3-8</sub>-cycloalkyl-C<sub>2-6</sub>-alkynyl, C<sub>4-8</sub>-cycloalkenyl-C<sub>1-6</sub>-alkyl, C<sub>4-8</sub>-cycloalkenyl-C<sub>2-6</sub>-alkenyl, C<sub>4-8</sub>-cycloalkenyl-C<sub>2-6</sub>-alkynyl, heterocyclyl-C<sub>1-6</sub>-alkyl, heterocyclyl-C<sub>2-6</sub>-alkenyl or heterocyclyl-C<sub>2-6</sub>-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from

-CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -SCF<sub>3</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>,  
 -SR<sup>21</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, -OC(O)NR<sup>21</sup>R<sup>22</sup>, -NR<sup>21</sup>C(O)R<sup>22</sup>,  
 -OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -C(O)R<sup>21</sup> and -C(O)OR<sup>21</sup>,

C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl and C<sub>2-6</sub>-alkynyl,

which may optionally be substituted with one or more substituents selected from -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>,  
 -SCF<sub>3</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>, -SR<sup>21</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>,  
 -OC(O)NR<sup>21</sup>R<sup>22</sup>, -NR<sup>21</sup>C(O)R<sup>22</sup>, -OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -C(O)R<sup>21</sup> and -C(O)OR<sup>21</sup>,

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C<sub>1-6</sub>-alkoxy, aryl-C<sub>1-6</sub>-alkyl, aryl-C<sub>2-6</sub>-alkenyl, aryl-C<sub>2-6</sub>-alkynyl, heteroaryl, heteroaryl-C<sub>1-6</sub>-alkyl, heteroaryl-C<sub>2-6</sub>-alkenyl or heteroaryl-C<sub>2-6</sub>-alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from

halogen, -CN, -CH<sub>2</sub>CN, -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>,  
 -OS(O)<sub>2</sub>CF<sub>3</sub>, -SCF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>, -SR<sup>21</sup>, -NR<sup>21</sup>S(O)<sub>2</sub>R<sup>22</sup>, -S(O)<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>,  
 -S(O)NR<sup>21</sup>R<sup>22</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -OS(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, -OC(O)NR<sup>21</sup>R<sup>22</sup>,  
 -NR<sup>21</sup>C(O)R<sup>22</sup>, -CH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -CH<sub>2</sub>OR<sup>21</sup>, -CH<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>,  
 -OC(O)R<sup>21</sup>, -C(O)R<sup>21</sup> and -C(O)OR<sup>21</sup>,

C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl and C<sub>2-6</sub>-alkynyl,

which may optionally be substituted with one or more substituents selected from -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>,  
 -SCF<sub>3</sub>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup>, -SR<sup>21</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>,  
 -OC(O)NR<sup>21</sup>R<sup>22</sup>, -NR<sup>21</sup>C(O)R<sup>22</sup>, -OCH<sub>2</sub>C(O)NR<sup>21</sup>R<sup>22</sup>, -C(O)R<sup>21</sup> and  
 -C(O)OR<sup>21</sup>,

wherein R<sup>21</sup> and R<sup>22</sup> independently are hydrogen, -CF<sub>3</sub>, C<sub>1-6</sub>-alkyl, tri-C<sub>1-6</sub>-alkylsilyl, C<sub>3-8</sub>-cycloalkyl, C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkyl, aryl, aryl-C<sub>1-6</sub>-alkyl or heteroaryl,

or R<sup>21</sup> and R<sup>22</sup> when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R<sup>16</sup> to R<sup>19</sup> when placed in adjacent positions together may form a bridge  
 -(CR<sup>16</sup>R<sup>17</sup>)<sub>a</sub>-O-(CR<sup>18</sup>R<sup>19</sup>)<sub>c</sub>-O-,

wherein

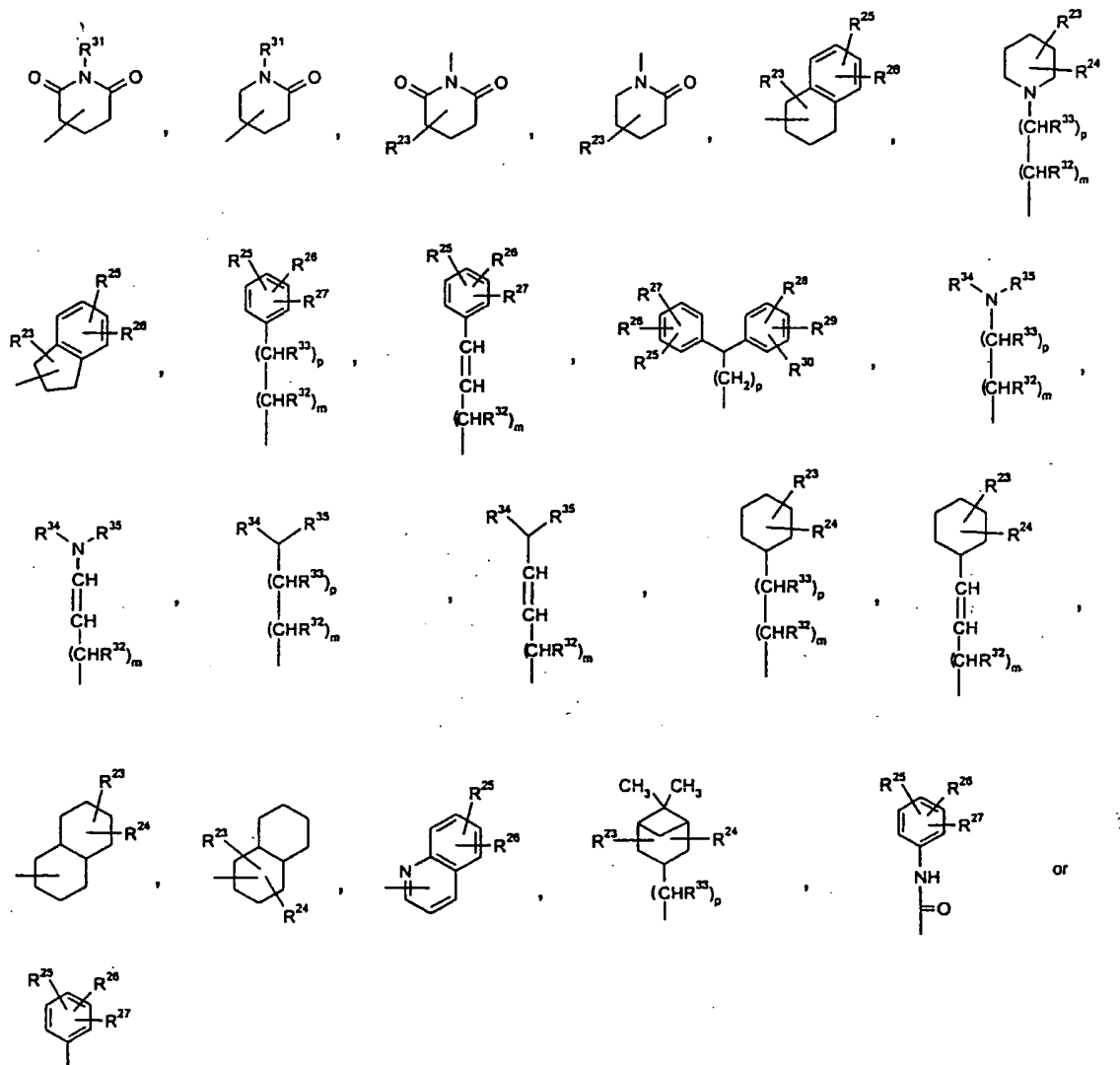
a is 0, 1 or 2,

c is 1 or 2,

R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup> and R<sup>19</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl or halogen,

R<sup>20</sup> and R<sup>20'</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl, C<sub>3-8</sub>-cycloalkyl or C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkyl,

E is a 3 to 9 membered mono- or bicyclic ring which may optionally contain one or two double bonds and which may optionally contain one or two heteroatoms selected from nitrogen, oxygen and sulfur, wherein one or two groups  $R^{23}$  and  $R^{24}$  may be attached to the same or different ring carbon atoms and wherein a group  $R^{31}$  may be attached to a ring nitrogen atom when present, or



wherein

10

m and p independently are 0, 1, 2, 3 or 4, with the proviso that when both m and p are present in the same formula at least one of m and p is different from 0,

R<sup>23</sup> and R<sup>24</sup> independently are

- hydrogen, -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -SCF<sub>3</sub>, -OR<sup>36</sup>, -NR<sup>36</sup>R<sup>37</sup>,  
 5 -SR<sup>36</sup>, -S(O)R<sup>36</sup>, -S(O)<sub>2</sub>R<sup>36</sup>, -C(O)NR<sup>36</sup>R<sup>37</sup>, -OC(O)NR<sup>36</sup>R<sup>37</sup>, -NR<sup>36</sup>C(O)R<sup>37</sup>,  
 -OCH<sub>2</sub>C(O)NR<sup>36</sup>R<sup>37</sup>, -C(O)R<sup>36</sup> or -C(O)OR<sup>36</sup>,

- C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl or C<sub>2-6</sub>-alkynyl,

10 which may optionally be substituted with one or more substituents selected from  
 -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -SCF<sub>3</sub>, -OR<sup>36</sup>, -NR<sup>36</sup>R<sup>37</sup>,  
 -SR<sup>36</sup>, -S(O)R<sup>36</sup>, -S(O)<sub>2</sub>R<sup>36</sup>, -C(O)NR<sup>36</sup>R<sup>37</sup>, -OC(O)NR<sup>36</sup>R<sup>37</sup>, -NR<sup>36</sup>C(O)R<sup>37</sup>,  
 -OCH<sub>2</sub>C(O)NR<sup>36</sup>R<sup>37</sup>, -C(O)R<sup>36</sup> and -C(O)OR<sup>36</sup>,

- 15 • C<sub>3-8</sub>-cycloalkyl, C<sub>3-8</sub>-cycloalkylidene, C<sub>4-8</sub>-cycloalkenyl, heterocyclyl, C<sub>3-8</sub>-cycloalkyl-  
 C<sub>1-6</sub>-alkyl, C<sub>3-8</sub>-cycloalkyl-C<sub>2-6</sub>-alkenyl, C<sub>3-8</sub>-cycloalkyl-C<sub>2-6</sub>-alkynyl, C<sub>4-8</sub>-cycloalkenyl-  
 C<sub>1-6</sub>-alkyl, C<sub>4-8</sub>-cycloalkenyl-C<sub>2-6</sub>-alkenyl, C<sub>4-8</sub>-cycloalkenyl-C<sub>2-6</sub>-alkynyl, heterocyclyl-  
 C<sub>1-6</sub>-alkyl, heterocyclyl-C<sub>2-6</sub>-alkenyl or heterocyclyl-C<sub>2-6</sub>-alkynyl,

20 of which the cyclic moieties optionally may be substituted with one or more substituents selected from

- CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -SCF<sub>3</sub>, -OR<sup>36</sup>, -NR<sup>36</sup>R<sup>37</sup>,  
 -SR<sup>36</sup>, -S(O)R<sup>36</sup>, -S(O)<sub>2</sub>R<sup>36</sup>, -C(O)NR<sup>36</sup>R<sup>37</sup>, -OC(O)NR<sup>36</sup>R<sup>37</sup>, -NR<sup>36</sup>C(O)R<sup>37</sup>,  
 25 -OCH<sub>2</sub>C(O)NR<sup>36</sup>R<sup>37</sup>, -C(O)R<sup>36</sup> and -C(O)OR<sup>36</sup>,

C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl and C<sub>2-6</sub>-alkynyl,

30 which may optionally be substituted with one or more substituents selected from -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>,  
 -SCF<sub>3</sub>, -OR<sup>36</sup>, -NR<sup>36</sup>R<sup>37</sup>, -SR<sup>36</sup>, -S(O)R<sup>36</sup>, -S(O)<sub>2</sub>R<sup>36</sup>, -C(O)NR<sup>36</sup>R<sup>37</sup>,  
 -OC(O)NR<sup>36</sup>R<sup>37</sup>, -NR<sup>36</sup>C(O)R<sup>37</sup>, -OCH<sub>2</sub>C(O)NR<sup>36</sup>R<sup>37</sup>, -C(O)R<sup>36</sup> and  
 -C(O)OR<sup>36</sup>,



- aryl, aryloxy, aroyl, aryl-C<sub>1-6</sub>-alkoxy, aryl-C<sub>1-6</sub>-alkyl, aryl-C<sub>2-6</sub>-alkenyl, aryl-C<sub>2-6</sub>-alkynyl, heteroaryl, heteroaryl-C<sub>1-6</sub>-alkyl, heteroaryl-C<sub>2-6</sub>-alkenyl or heteroaryl-C<sub>2-6</sub>-alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from

halogen, -CN, -CH<sub>2</sub>CN, -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -OS(O)<sub>2</sub>CF<sub>3</sub>, -SCF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>36</sup>, -NR<sup>36</sup>R<sup>37</sup>, -SR<sup>36</sup>, -NR<sup>36</sup>S(O)<sub>2</sub>R<sup>37</sup>, -S(O)<sub>2</sub>NR<sup>36</sup>R<sup>37</sup>, -S(O)NR<sup>36</sup>R<sup>37</sup>, -S(O)R<sup>36</sup>, -S(O)<sub>2</sub>R<sup>36</sup>, -OS(O)<sub>2</sub>R<sup>36</sup>, -C(O)NR<sup>36</sup>R<sup>37</sup>, -OC(O)NR<sup>36</sup>R<sup>37</sup>, -NR<sup>36</sup>C(O)R<sup>37</sup>, -CH<sub>2</sub>C(O)NR<sup>36</sup>R<sup>37</sup>, -CH<sub>2</sub>C(O)NR<sup>36</sup>R<sup>37</sup>, -CH<sub>2</sub>OR<sup>36</sup>, -CH<sub>2</sub>NR<sup>36</sup>R<sup>37</sup>, -OC(O)R<sup>36</sup>, -C(O)R<sup>36</sup> and -C(O)OR<sup>36</sup>,

C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl and C<sub>2-6</sub>-alkynyl,

which may optionally be substituted with one or more substituents selected from -CHF<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CF<sub>3</sub>, -OCF<sub>2</sub>CHF<sub>2</sub>, -SCF<sub>3</sub>, -OR<sup>36</sup>, -NR<sup>36</sup>R<sup>37</sup>, -SR<sup>36</sup>, -S(O)R<sup>36</sup>, -S(O)<sub>2</sub>R<sup>36</sup>, -C(O)NR<sup>36</sup>R<sup>37</sup>, -OC(O)NR<sup>36</sup>R<sup>37</sup>, -NR<sup>36</sup>C(O)R<sup>37</sup>, -OCH<sub>2</sub>C(O)NR<sup>36</sup>R<sup>37</sup>, -C(O)R<sup>36</sup> and -C(O)OR<sup>36</sup>,

wherein R<sup>36</sup> and R<sup>37</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl or aryl,

of which the aryl moiety optionally may be substituted with one or more substituents selected from halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>38</sup>, -NR<sup>38</sup>R<sup>39</sup> and C<sub>1-6</sub>-alkyl,

wherein R<sup>38</sup> and R<sup>39</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl,

or R<sup>36</sup> and R<sup>37</sup> when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or R<sup>23</sup> and R<sup>24</sup> when attached to the same ring carbon atom or different ring carbon atoms together may form a radical -O-(CH<sub>2</sub>)<sub>i</sub>-CR<sup>40</sup>R<sup>41</sup>-(CH<sub>2</sub>)<sub>j</sub>-O-, -(CH<sub>2</sub>)<sub>i</sub>-CR<sup>40</sup>R<sup>41</sup>-(CH<sub>2</sub>)<sub>j</sub>- or



wherein

5 t and l independently are 0, 1, 2, 3, 4 or 5,

R<sup>40</sup> and R<sup>41</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl,

10 R<sup>25</sup> to R<sup>30</sup> independently are hydrogen, halogen, -CN, -CF<sub>3</sub>, -NO<sub>2</sub>, -OR<sup>42</sup>, -NR<sup>42</sup>R<sup>43</sup>, C<sub>1-6</sub>-alkyl, C<sub>3-6</sub>-cycloalkyl or C<sub>4-6</sub>-cycloalkenyl,

wherein R<sup>42</sup> and R<sup>43</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl, or

15 R<sup>42</sup> and R<sup>43</sup> when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

20 R<sup>31</sup>, R<sup>32</sup> and R<sup>33</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl,

R<sup>34</sup> and R<sup>35</sup> independently are

- hydrogen, C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy, C<sub>1-6</sub>-alkanoyl, -C(O)NR<sup>44</sup>R<sup>45</sup> or -S(O)<sub>2</sub>R<sup>45</sup>,
- 25 • aryl, aroyl, aryl-C<sub>1-6</sub>-alkoxy, aryl-C<sub>1-6</sub>-alkanoyl or aryl-C<sub>1-6</sub>-alkyl,

of which the aryl moieties optionally may be substituted with one or more substituents selected from halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OR<sup>44</sup>, -NR<sup>44</sup>R<sup>45</sup> and C<sub>1-6</sub>-alkyl,

30 wherein R<sup>44</sup> and R<sup>45</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl, or

R<sup>34</sup> and R<sup>35</sup> when attached to a carbon atom together with the said carbon atom may form a 3 to 8 membered cyclic ring optionally containing one or two heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds, or

35

R<sup>34</sup> and R<sup>35</sup> when attached to a nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds.

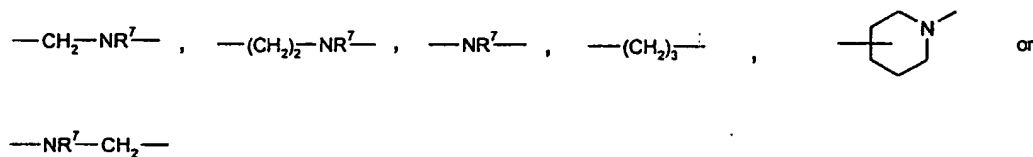
5 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein V is -C(O)OH, -S(O)<sub>2</sub>OH, -C(O)NHOH or 5-tetrazolyl.

3. A compound according to claim 2, wherein V is -C(O)OH.

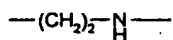
4. A compound according to claim 2, wherein V is 5-tetrazolyl.

15 5. A compound according to any one of the claims 1 to 4, wherein A is

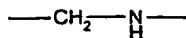


wherein  $R^7$  is as defined in claim 1.

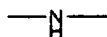
6. A compound according to claim 5, wherein A is



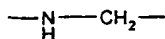
25 7. A compound according to claim 5, wherein A is



8. A compound according to claim 5, wherein A is



9. A compound according to claim 5, wherein A is

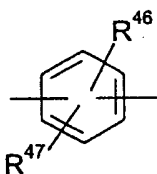


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10. A compound according to any one of the claims 1 to 9, wherein Y is  $\text{—C(O)—}$ .

11. A compound according to any one of the claims 1 to 9, wherein Y is a valence bond.

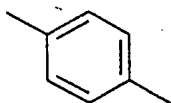
10 12. A compound according to any one of the claims 1 to 11, wherein Z is



wherein  $\text{R}^{46}$  and  $\text{R}^{47}$  are as defined in claim 1.

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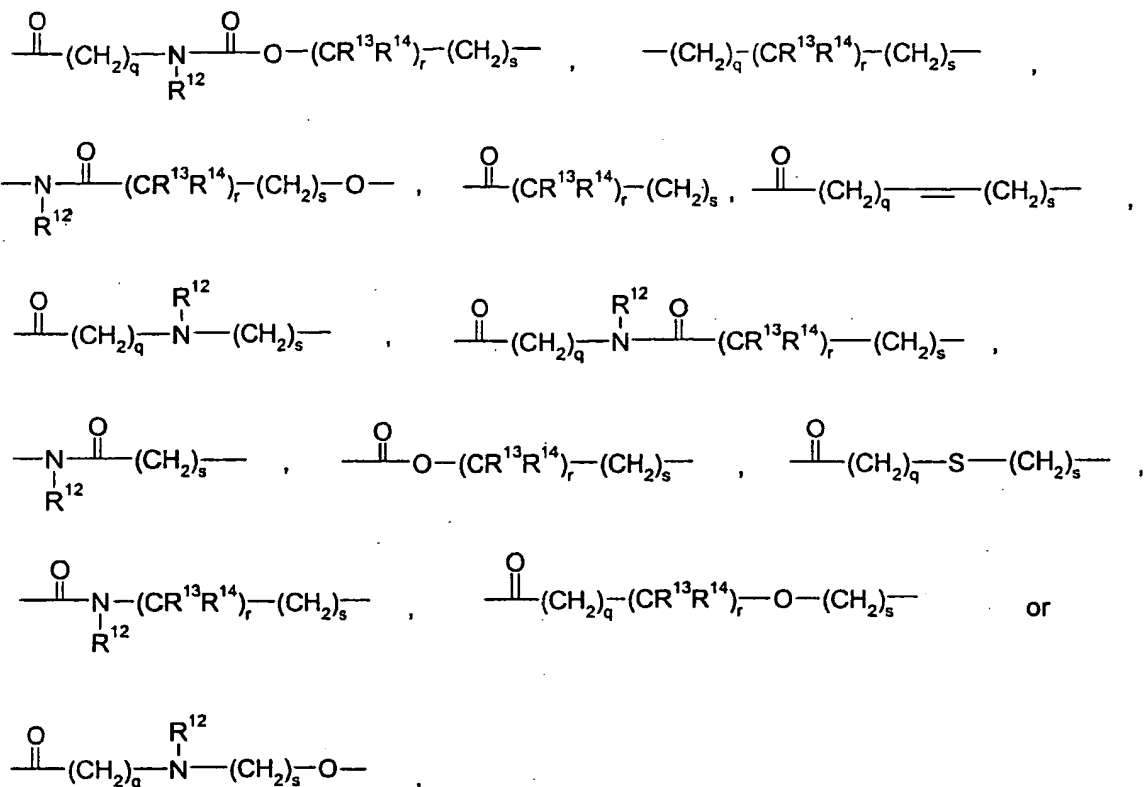
13. A compound according to claim 12, wherein Z is



20 14. A compound according to any one of the claims 1 to 13, wherein  $\text{R}^1$  is hydrogen.

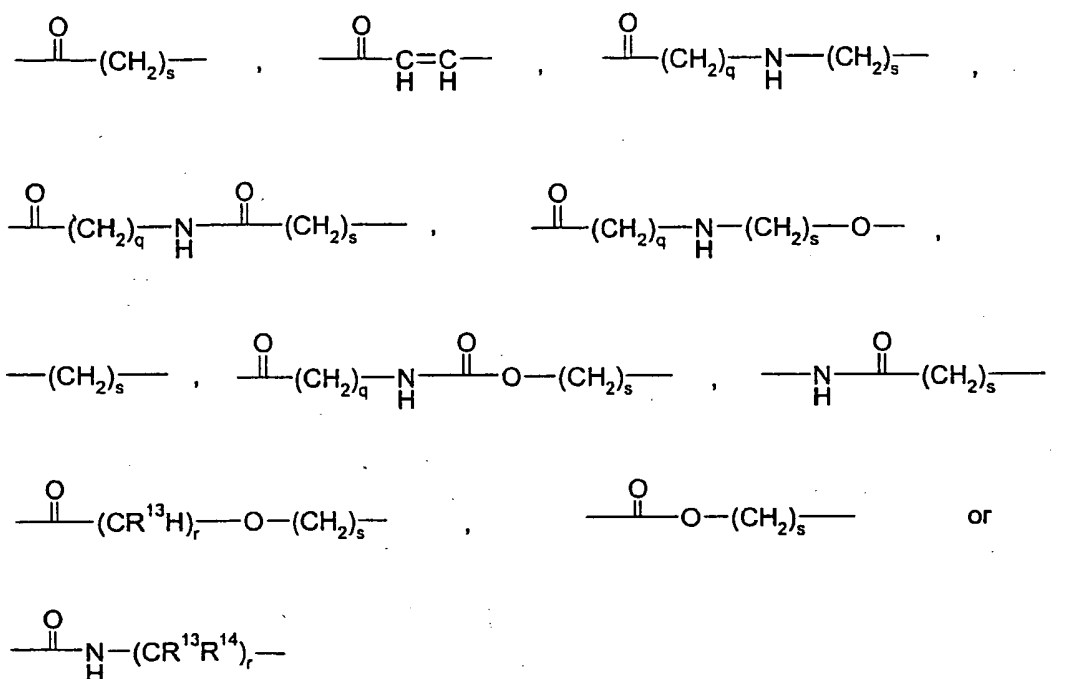
15. A compound according to any one of the claims 1 to 13, wherein  $\text{R}^1$  is methyl.

16. A compound according to any one of the claims 1 to 15, wherein X is



5 wherein q, r, s, R<sup>12</sup>, R<sup>13</sup> and R<sup>14</sup> are as defined in claim 1.

17. A compound according to claim 16, wherein X is



5 wherein q is 0 or 1, r is 0 or 1, s is 0, 1 or 2, and R<sup>13</sup> is hydrogen or C<sub>1-6</sub>-alkyl.

18. A compound according to claim 17, wherein X is -C(O)NH-, -C(O)NHCH<sub>2</sub>-,  
-C(O)NHCH(CH<sub>3</sub>)-, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>-, -C(O)CH<sub>2</sub>-, -C(O)CH=CH-, -(CH<sub>2</sub>)<sub>s</sub>-, -C(O)-, -C(O)O-  
or -NHC(O)-, wherein s is 0 or 1.

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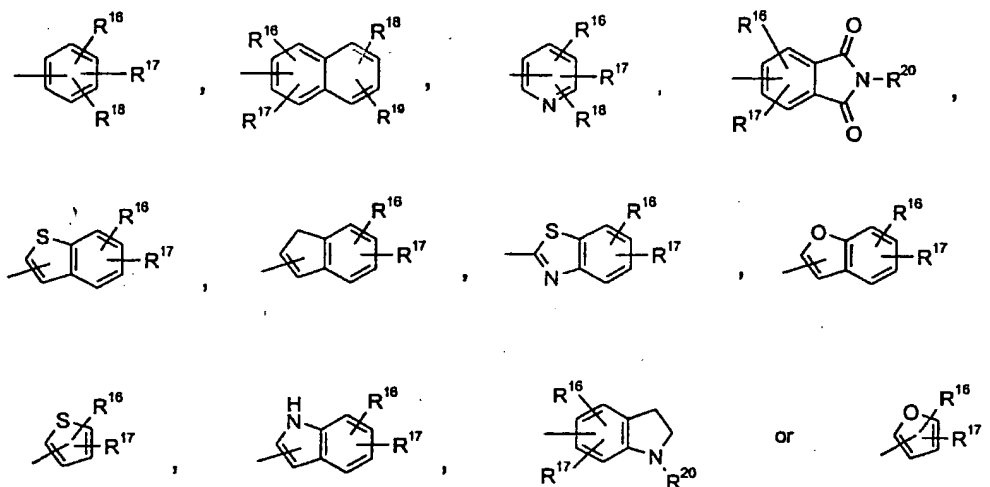
19. A compound according to claim 18, wherein X is -C(O)NH-, -C(O)NHCH<sub>2</sub>-,  
-C(O)NHCH(CH<sub>3</sub>)-, -C(O)NHCH<sub>2</sub>CH<sub>2</sub>-, -C(O)CH<sub>2</sub>-, -CH<sub>2</sub>-, -C(O)- or -NHC(O)-.

20. A compound according to claim 19, wherein X is -C(O)NH-.

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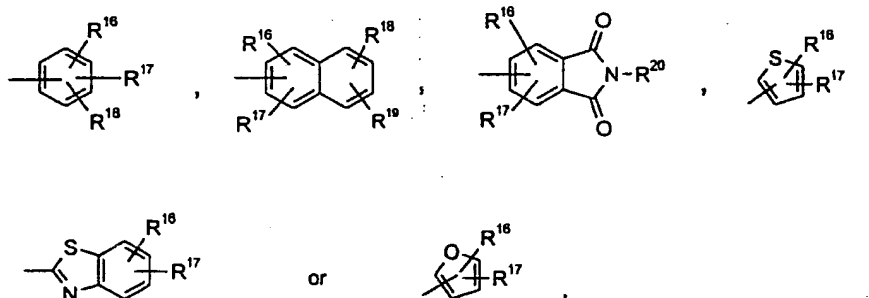
21. A compound according to claim 19, wherein X is -C(O)NHCH(CH<sub>3</sub>)-.

22. A compound according to any one of the claims 1 to 21, wherein D is



5 wherein  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$  and  $R^{20}$  are as defined in claim 1.

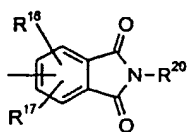
23. A compound according to claim 22, wherein D is



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wherein  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$  and  $R^{20}$  are as defined in claim 1.

24. A compound according to claim 23, wherein D is



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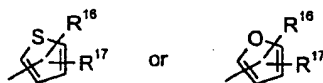
wherein  $R^{16}$ ,  $R^{17}$  and  $R^{20}$  are as defined in claim 1.

25. A compound according to claim 24, wherein  $R^{16}$  and  $R^{17}$  are both hydrogen and  $R^{20}$  is  $C_{1-6}$ -alkyl or  $C_{3-8}$ -cycloalkyl- $C_{1-6}$ -alkyl.

5 26. A compound according to claim 24 or 25, wherein  $R^{20}$  is cyclopropylmethyl, butyl or isopropyl.

27. A compound according to claim 26, wherein  $R^{20}$  is isopropyl.

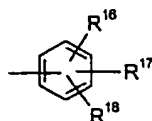
10 28. A compound according to claim 23, wherein D is



wherein  $R^{16}$  and  $R^{17}$  are as defined in claim 1.

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29. A compound according to claim 23, wherein D is



20 wherein  $R^{16}$ ,  $R^{17}$  and  $R^{18}$  are as defined in claim 1.

30. A compound according to any one of the claims 22, 23, 28 or 29, wherein  $R^{16}$ ,  $R^{17}$  and  $R^{18}$  independently are

25 hydrogen, halogen, -CN, -NO<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, hydroxy, -SCF<sub>3</sub>,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkyl substituted with hydroxy,  $C_{1-6}$ -alkyl substituted with -S(O)<sub>2</sub>R<sup>21</sup>,  $C_{1-6}$ -alkoxy, -S- $C_{1-6}$ -alkyl, -C(O)OR<sup>21</sup>, -C(O)R<sup>21</sup>, -CH<sub>2</sub>(O)R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -S(O)<sub>2</sub>CF<sub>3</sub>, -S(O)<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>,  $C_{3-8}$ -cycloalkyl,  $C_{3-8}$ -cycloalkyl- $C_{1-6}$ -alkoxy,  $C_{3-8}$ -cycloalkyl- $C_{1-6}$ -alkylthio or  $C_{3-8}$ -cycloalkylthio,

30 wherein  $R^{21}$  and  $R^{22}$  independently are hydrogen,  $C_{1-6}$ -alkyl, tri- $C_{1-6}$ -alkylsilyl,  $C_{3-8}$ -cycloalkyl,  $C_{3-8}$ -cycloalkyl- $C_{1-6}$ -alkyl, phenyl, phenyl- $C_{1-6}$ -alkyl, 2,3-dihydroindolyl or isoindolyl, or  $R^{21}$  and  $R^{22}$  together with the nitrogen atom to which they are attached form a piperidine ring,



phenoxy, phenoxycarbonyl, phenyl, phenyl-C<sub>1-6</sub>-alkoxy, phenyl-C<sub>1-6</sub>-alkyl, furanyl, tetrazolyl, benzoxazolyl or oxadiazolyl, of which the ring systems optionally may be substituted with halogen, -CN, -CF<sub>3</sub>, -OCF<sub>3</sub>, -NO<sub>2</sub>, -C(O)OR<sup>21</sup>, -OR<sup>21</sup>, -NR<sup>21</sup>R<sup>22</sup> or C<sub>1-6</sub>-alkyl, wherein R<sup>21</sup> and  
5 R<sup>22</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl, or

wherein R<sup>16</sup> and R<sup>17</sup> in adjacent positions form the radical -O-CH<sub>2</sub>-O-, -CF<sub>2</sub>-O-CF<sub>2</sub>-O- or -O-CF<sub>2</sub>-CF<sub>2</sub>-O-, and R<sup>18</sup> is hydrogen.

10 31. A compound according to claim 30, wherein R<sup>16</sup>, R<sup>17</sup> and R<sup>18</sup> independently are

hydrogen, halogen, -CN, -NO<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -SCF<sub>3</sub>, C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkyl substituted with hydroxy, C<sub>1-6</sub>-alkyl substituted with -S(O)<sub>2</sub>R<sup>21</sup>, C<sub>1-6</sub>-alkoxy, -S-C<sub>1-6</sub>-alkyl, -C(O)OR<sup>21</sup>, -C(O)R<sup>21</sup>, -CH<sub>2</sub>(O)R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, -S(O)R<sup>21</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -S(O)<sub>2</sub>CF<sub>3</sub>, -S(O)<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>, C<sub>3-8</sub>-cyclo-  
15 alkyl-C<sub>1-6</sub>-alkoxy, C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkylthio or C<sub>3-8</sub>-cycloalkylthio,

wherein R<sup>21</sup> and R<sup>22</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl, tri-C<sub>1-6</sub>-alkylsilyl, C<sub>3-8</sub>-cycloalkyl, C<sub>3-8</sub>-cycloalkyl-C<sub>1-6</sub>-alkyl, phenyl or 2,3-dihydroindolyl, or R<sup>21</sup> and R<sup>22</sup> together with the nitrogen atom to which they are attached form a piperidine ring,

20

phenoxy, phenyl, benzyl, furanyl, tetrazolyl, benzoxazolyl or oxadiazolyl, of which the ring systems optionally may be substituted with halogen, -C(O)OR<sup>21</sup> or C<sub>1-6</sub>-alkyl, wherein R<sup>21</sup> is hydrogen or C<sub>1-6</sub>-alkyl, or

25 wherein R<sup>16</sup> and R<sup>17</sup> in adjacent positions form the radical -CF<sub>2</sub>-O-CF<sub>2</sub>-O- or -O-CF<sub>2</sub>-CF<sub>2</sub>-O-, and R<sup>18</sup> is hydrogen.

32. A compound according to claim 31, wherein R<sup>16</sup>, R<sup>17</sup> and R<sup>18</sup> independently are

30 hydrogen, halogen, -CN, -NO<sub>2</sub>, -CF<sub>3</sub>, -OCF<sub>3</sub>, -SCF<sub>3</sub>, C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkyl substituted with hydroxy, C<sub>1-6</sub>-alkoxy, -S-C<sub>1-6</sub>-alkyl, -C(O)OR<sup>21</sup>, -C(O)R<sup>21</sup>, -CH<sub>2</sub>(O)R<sup>21</sup>, -C(O)NR<sup>21</sup>R<sup>22</sup>, -S(O)<sub>2</sub>R<sup>21</sup>, -(O)<sub>2</sub>CF<sub>3</sub> or -S(O)<sub>2</sub>NR<sup>21</sup>R<sup>22</sup>,

wherein R<sup>21</sup> and R<sup>22</sup> independently are hydrogen, C<sub>1-6</sub>-alkyl, tri-C<sub>1-6</sub>-alkylsilyl, phenyl or  
35 2,3-dihydroindolyl,

phenoxy, phenyl, benzyl, furanyl, tetrazolyl, benzoxazolyl or oxadiazolyl, of which the ring systems optionally may be substituted with halogen,  $-C(O)OR^{21}$  or  $C_{1-6}$ -alkyl, wherein  $R^{21}$  is hydrogen or  $C_{1-6}$ -alkyl, or

5

wherein  $R^{16}$  and  $R^{17}$  in adjacent positions form the radical  $-CF_2-O-CF_2-O-$  or  $-O-CF_2-CF_2-O-$ , and  $R^{18}$  is hydrogen.

10

33. A compound according to claim 32, wherein  $R^{16}$ ,  $R^{17}$  and  $R^{18}$  independently are hydrogen, halogen,  $-CN$ ,  $-NO_2$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-SCF_3$ ,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy,  $-S-C_{1-6}$ -alkyl,  $-C(O)OC_{1-6}$ -alkyl,  $-S(O)_2C_{1-6}$ -alkyl,  $-S(O)_2CF_3$ ,  $-C(O)N(C_{1-6}$ -alkyl)( $C_{1-6}$ -alkyl),  $-S(O)_2N(phenyl)(C_{1-6}$ -alkyl),  $-C(=O)C_{1-6}$ -alkyl,  $-CH_2OH$ ,  $-CH_2O(tri-C_{1-6}$ -alkylsilyl)

15 yl), 2,3-dihydroindol-1-ylsulfonyl, phenoxy, phenyl, 4-chlorophenyl, 1,3,5-trimethylbenzyl, benzoxazolyl, 2-methyltetrazol-5-yl, 2-methyl-3-methoxycarbonylfuran-5-yl or 3-isopropyl-[1,2,4]oxadiazol-5-yl).

15

34. A compound according to any one of the claims 30 to 33, wherein one of  $R^{16}$  to  $R^{18}$  is hydrogen.

20

35. A compound according to any one of the claims 30 to 33, wherein two of  $R^{16}$  to  $R^{18}$  are hydrogen.

25

36. A compound according to claim 30, wherein  $R^{16}$  and  $R^{17}$  are both hydrogen and  $R^{18}$  is  $-OCF_3$ ,  $-SCF_3$ ,  $-CF_3$ ,  $-S(O)_2CH_3$ , phenyl, halogen,  $C_{1-6}$ -alkyl, nitro,  $-S-C_{1-6}$ -alkyl or  $-S(O)_2NR^{21}R^{22}$ , wherein  $R^{21}$  is  $C_{1-6}$ -alkyl and  $R^{22}$  is phenyl.

37. A compound according to claim 30, wherein  $R^{16}$  and  $R^{17}$  are both hydrogen and  $R^{18}$  is  $-OCF_3$  or halogen.

30

38. A compound according to claim 30, wherein  $R^{16}$  is hydrogen and  $R^{17}$  and  $R^{18}$  are both halogen or are both  $-CF_3$ .

39. A compound according to claim 30, wherein  $R^{16}$  is hydrogen,  $R^{17}$  is  $-CF_3$  and  $R^{18}$  is halogen,  $-CN$ ,  $C_{1-6}$ -alkoxy or  $-OCF_3$ .

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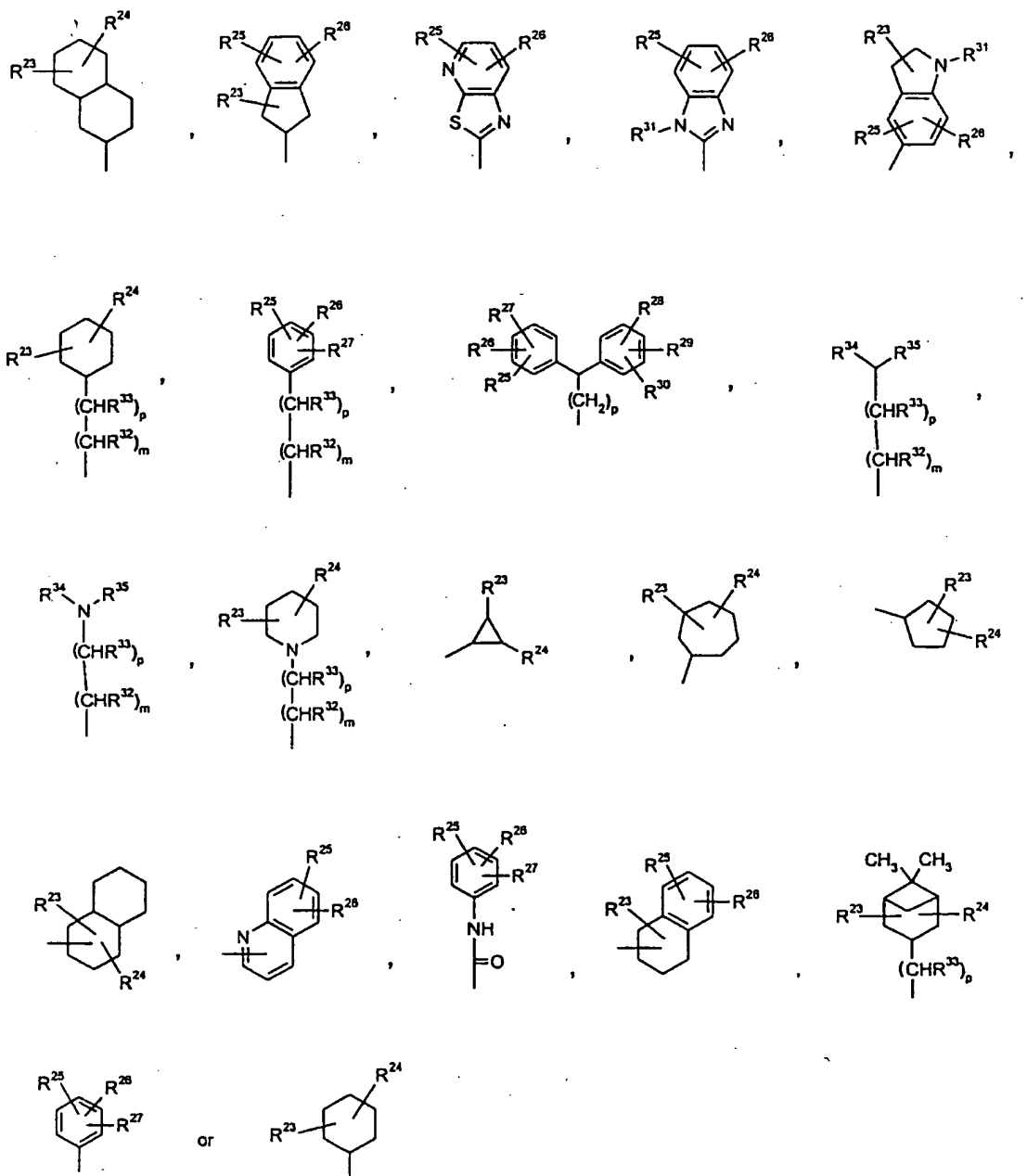
40. A compound according to claim 30, wherein  $R^{16}$  is hydrogen,  $R^{17}$  is  $-OCF_3$  and  $R^{18}$  is  $-S(O)_2CH_3$ ,  $-CH_2O$ -tri- $C_{1-6}$ -alkylsilyl, benzoxazolyl or  $-CH_2OH$ .
41. A compound according to claim 30, wherein  $R^{16}$  is hydrogen,  $R^{17}$  is  $C_{1-6}$ -alkyl and  $R^{18}$  is  
5  $-S(O)_2NR^{21}R^{22}$ , wherein  $R^{21}$  is  $C_{1-6}$ -alkyl and  $R^{22}$  is phenyl.
42. A compound according to claim 30, wherein  $R^{16}$ ,  $R^{17}$  and  $R^{18}$  are selected from hydrogen,  $-OCF_3$ ,  $-CF_3$ ,  $-Br$ ,  $-F$  and  $-Cl$ .



wherein

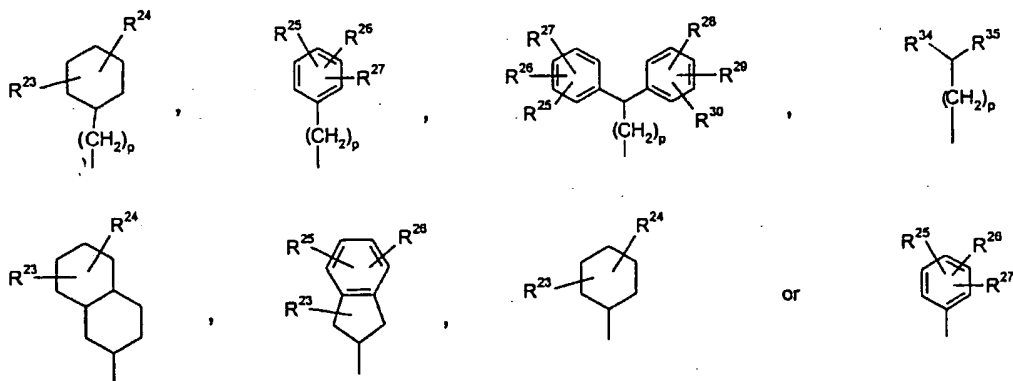
m, p and  $R^{23}$  to  $R^{35}$  are as defined in claim 1.

5 44. A compound according to claim 43, wherein E is



wherein m, p and  $R^{23}$  to  $R^{35}$  are as defined in claim 1.

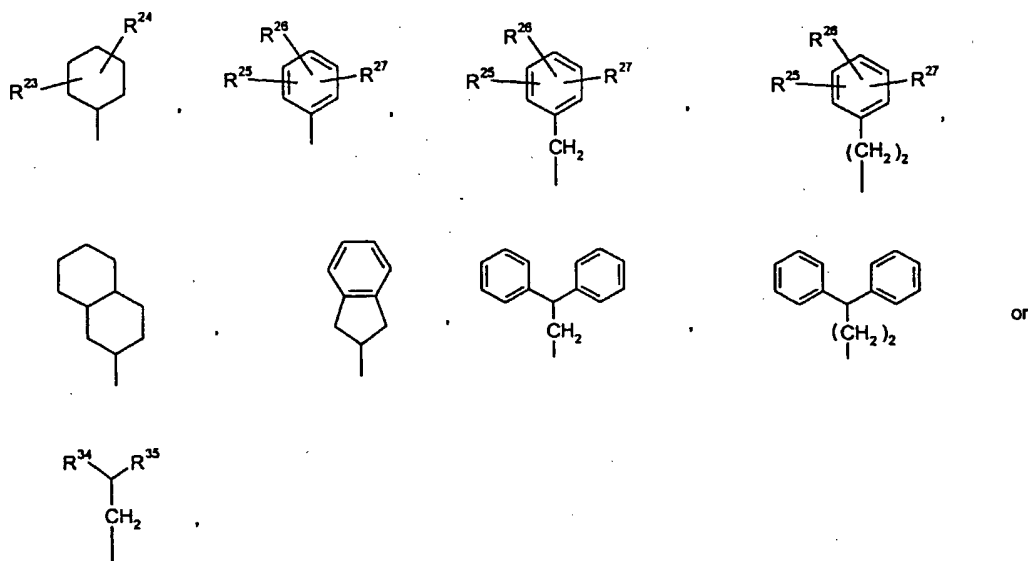
45. A compound according to claim 44, wherein E is



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wherein p, R<sup>23</sup>, R<sup>24</sup>, R<sup>25</sup>, R<sup>26</sup>, R<sup>27</sup>, R<sup>28</sup>, R<sup>29</sup>, R<sup>30</sup>, R<sup>34</sup> and R<sup>35</sup> are as defined in claim 1.

46. A compound according to claim 45, wherein E is



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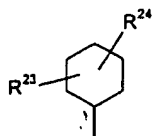
wherein R<sup>23</sup>, R<sup>24</sup>, R<sup>25</sup>, R<sup>26</sup>, R<sup>27</sup>, R<sup>34</sup> and R<sup>35</sup> are as defined in claim 1.

47. A compound according to claim 46, wherein R<sup>34</sup> and R<sup>35</sup> independently are C<sub>1-6</sub>-alkyl, hydrogen or C<sub>1-6</sub>-alkoxy.

15

48. A compound according to claim 47, wherein  $R^{34}$  and  $R^{35}$  are both  $C_{1-6}$ -alkyl.

49. A compound according to claim 45, wherein E is

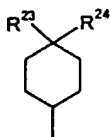


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wherein  $R^{23}$  and  $R^{24}$  are as defined in claim 1.

50. A compound according to claim 49, wherein E is

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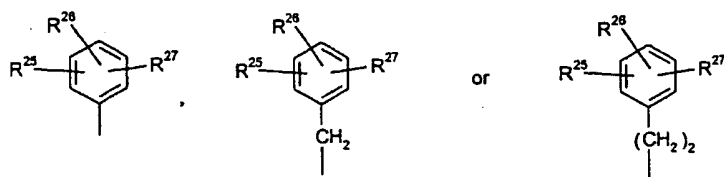
wherein  $R^{23}$  and  $R^{24}$  are as defined in claim 1.

15 51. A compound according to claim 49 or 50, wherein  $R^{23}$  and  $R^{24}$  independently are selected from hydrogen,  $C_{1-6}$ -alkyl,  $C_{3-8}$ -cycloalkyl,  $C_{3-8}$ -cycloalkylidene, phenoxy, phenyl,  $-C(O)NR^{36}R^{37}$  and  $-OC(O)NH$ -phenyl, of which the phenyl moiety optionally may be substituted with  $-OCF_3$ , wherein  $R^{36}$  and  $R^{37}$  are as defined in claim 1, or  $R^{23}$  and  $R^{24}$  together form the radical  $-(CH_2)_t-CR^{40}R^{41}-(CH_2)_l-$ ,  $-O-(CH_2)_t-CR^{40}R^{41}-(CH_2)_l-O-$ ,  $-S-(CH_2)_t-CR^{40}R^{41}-(CH_2)_l-S-$ ,  
20 wherein  $t, l, R^{40}$  and  $R^{41}$  are as defined in claim 1.

52. A compound according to claim 51, wherein  $R^{23}$  is hydrogen and  $R^{24}$  is  $C_{1-6}$ -alkyl such as *tert*-butyl or  $C_{3-8}$ -cycloalkyl such as cyclohexyl, wherein  $R^{23}$  and  $R^{24}$  are both  $C_{1-6}$ -alkyl or wherein  $R^{23}$  and  $R^{24}$  together form the radical  $-(CH_2)_5-$ .

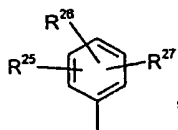
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53. A compound according to claim 46, wherein E is



5 wherein  $R^{25}$ ,  $R^{26}$  and  $R^{27}$  are as defined in claim 1.

54. A compound according to claim 53, wherein E is



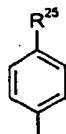
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wherein  $R^{25}$ ,  $R^{26}$  and  $R^{27}$  are as defined in claim 1.

55. A compound according to claim 53 or 54, wherein  $R^{25}$ ,  $R^{26}$  and  $R^{27}$  independently are selected from hydrogen, halogen,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkoxy,  $C_{3-8}$ -cycloalkyl,  $C_{4-8}$ -cycloalkenyl,  $-CF_3$ ,

15  $-OCF_3$  or  $-NR^{42}R^{43}$ , wherein  $R^{42}$  and  $R^{43}$  are as defined in claim 1.

56. A compound according to claim 55, wherein E is

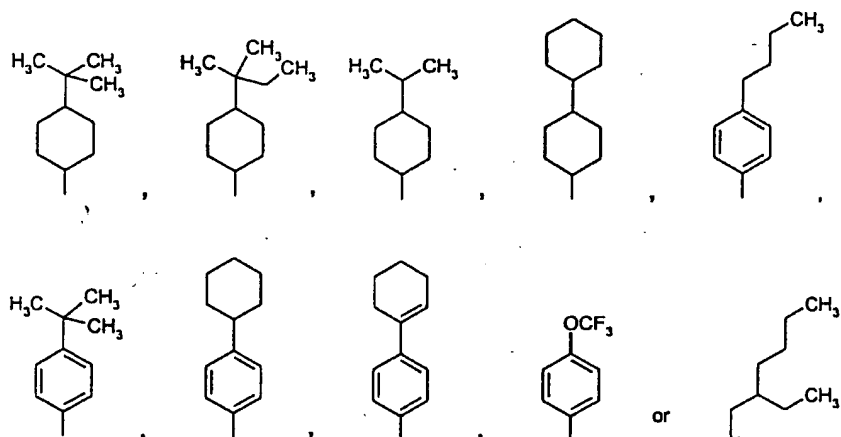


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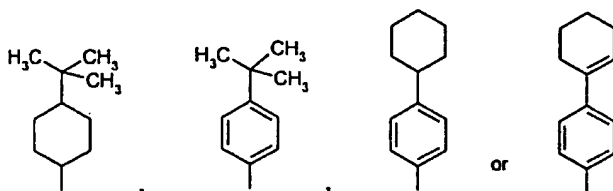
wherein  $R^{25}$  is  $-OCF_3$ ,  $-CF_3$ ,  $C_{1-6}$ -alkyl such as *tert*-butyl, piperidyl,  $C_{3-8}$ -cycloalkyl such as cyclohexyl or  $C_{4-8}$ -cycloalkenyl such as cyclohexenyl.



57. A compound according to claim 46, wherein E is

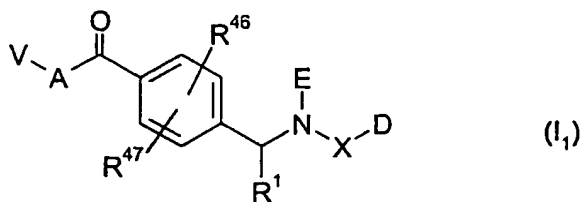


5 58. A compound according to claim 57, wherein E is



59. A compound according to claim 1 of the general formula (I<sub>1</sub>):

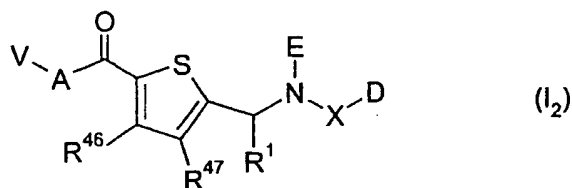
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wherein V, A, R<sup>46</sup>, R<sup>47</sup>, R<sup>1</sup>, E, X and D are as defined in claim 1 or in any one of the preceding claims.

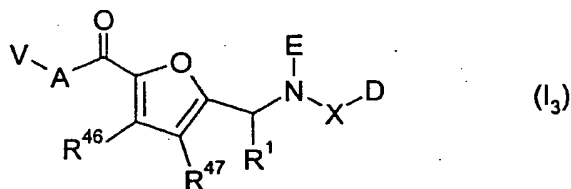
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60. A compound according to claim 1 of the general formula (I<sub>2</sub>):



5 wherein V, A, R<sup>46</sup>, R<sup>47</sup>, R<sup>1</sup>, E, X and D are as defined in claim 1 or in any one of the preceding claims.

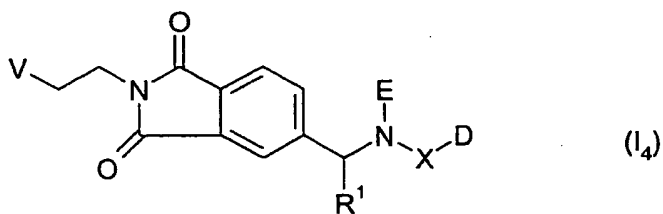
61. A compound according to claim 1 of the general formula (I<sub>3</sub>):



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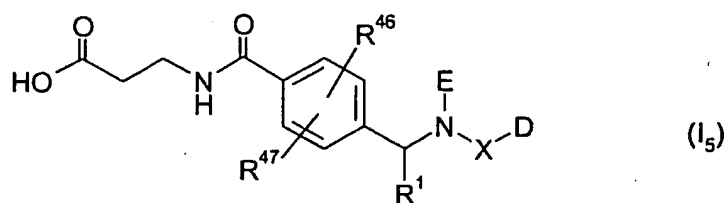
wherein V, A, R<sup>46</sup>, R<sup>47</sup>, R<sup>1</sup>, E, X and D are as defined in claim 1 or in any one of the preceding claims.

15 62. A compound according to claim 1 of the general formula (I<sub>4</sub>):



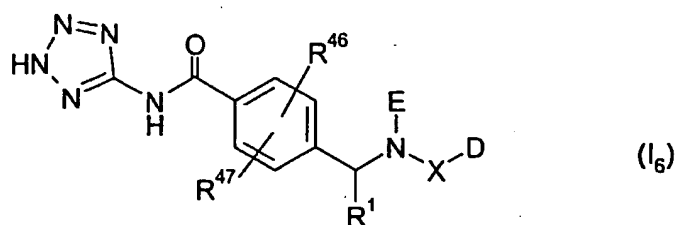
20 wherein V is -C(O)OR<sup>2</sup>, -C(O)NR<sup>2</sup>R<sup>3</sup> or -C(O)NR<sup>2</sup>OR<sup>3</sup>, and R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, E, X and D are as defined in claim 1 or in any one of the preceding claims.

63. A compound according to claim 1 of the general formula (I<sub>5</sub>):



5 wherein R<sup>46</sup>, R<sup>47</sup>, R<sup>1</sup>, E, X and D are as defined in claim 1 or in any one of the preceding claims.

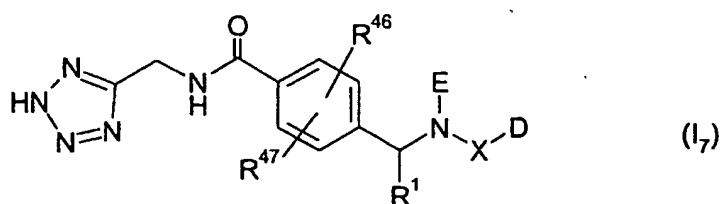
64. A compound according to claim 1 of the general formula (I<sub>6</sub>):



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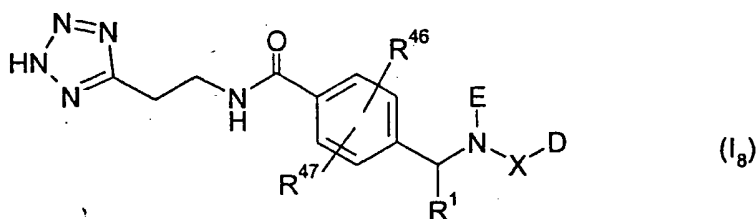
wherein R<sup>46</sup>, R<sup>47</sup>, R<sup>1</sup>, E, X and D are as defined in claim 1 or in any one of the preceding claims.

15 65. A compound according to claim 1 of the general formula (I<sub>7</sub>):



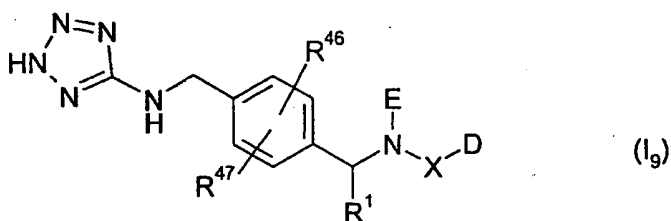
20 wherein R<sup>46</sup>, R<sup>47</sup>, R<sup>1</sup>, E, X and D are as defined in claim 1 or in any one of the preceding claims.

66. A compound according to claim 1 of the general formula (I<sub>8</sub>):



5 wherein R<sup>46</sup>, R<sup>47</sup>, R<sup>1</sup>, E, X and D are as defined in claim1 or in any one of the preceding claims.

67. A compound according to claim 1 of the general formula (I<sub>9</sub>):



wherein R<sup>46</sup>, R<sup>47</sup>, R<sup>1</sup>, E, X and D are as defined in claim 1 or in any one of the preceding claims.

15 68. A compound according to anyone of the claims 59 to 61 or 63 to 67, wherein R<sup>46</sup> and R<sup>47</sup> are both hydrogen.

69. A compound according to any one of the preceding claims, which has an  $IC_{50}$  value of no greater than 5  $\mu M$  as determined by the Glucagon Binding Assay (I), Glucagon Binding  
20 Assay (II) or Glucagon Binding Assay (III) disclosed herein.

70. A compound according to claim 69 characterized by having a glucagon antagonistic activity as determined by the Glucagon Binding Assay (I), Glucagon Binding Assay (II) or Glucagon Binding Assay (III) disclosed herein corresponding to an  $IC_{50}$  value of less than 1  $\mu$ M, preferably of less than 500 nM and even more preferred of less than 100 nM.

71. A compound according to any one of the preceding claims, which is an agent useful for the treatment and/or prevention of an indication selected from the group consisting of hyperglycemia, IGT, Type 2 diabetes, Type 1 diabetes and obesity.

5 72. A compound according to any one of the claims 1 to 71 for use as a medicament.

73. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 1 to 71 together with one or more pharmaceutically acceptable carriers or excipients.

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74. A pharmaceutical composition according to claim 73 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg and especially preferred from about 0.5 mg to about 200 mg of the compound according to any one of the claims 1 to 71.

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75. Use of a compound according to any one of the claims 1 to 71 for the preparation of a medicament for the treatment and/or prevention of disorders or diseases, wherein a glucagon antagonistic action is beneficial.

20 76. Use of a compound according to any one of the claims 1 to 71 for the preparation of a medicament for the treatment and/or prevention of glucagon-mediated disorders and diseases.

25 77. Use of a compound according to any one of the claims 1 to 71 for the manufacture of a medicament for the treatment and/or prevention of hyperglycemia.

78. Use of a compound according to any one of the claims 1 to 71 for the manufacture of a medicament for lowering blood glucose in a mammal.

30 79. Use of a compound according to any one of the claims 1 to 71 for the preparation of a medicament for the treatment and/or prevention of IGT.

80. Use of a compound according to any one of the claims 1 to 71 for the preparation of a medicament for the treatment and/or prevention of Type 2 diabetes.

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81. Use according to claim 80 for the preparation of a medicament for the delaying or prevention of the progression from IGT to Type 2 diabetes.

5 82. Use according to claim 80 for the preparation of a medicament for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

83. Use of a compound according to any one of the claims 1 to 71 for the preparation of a medicament for the treatment and/or prevention of Type 1 diabetes.

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84. Use according to any one of the claims 75 to 83 in a regimen which additionally comprises treatment with another antidiabetic agent.

15 85. Use of a compound according to any one of the claims 1 to 71 for the preparation of a medicament for the treatment and/or prevention of obesity.

86. Use of a compound according to any one of the claims 1 to 71 for the preparation of a medicament for the treatment and/or prevention of obesity in a regimen which additionally comprises treatment with another antiobesity agent.

20

87. A method for the treatment and/or prevention of disorders or diseases mediated by a glucagon antagonistic action, the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 1 to 71 or a pharmaceutical composition according to claim 73 or 74.

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88. The method according to claim 87, wherein the effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg, preferably from about 0.1 mg to about 1000 mg and especially preferred from about 0.5 mg to about 500 mg per day.

30

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 00/00264

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 237/32, C07C 243/24, C07C 271/40, C07C 275/28, C07D 209/48,  
C07D 257/04, C07D 333/04, A61K 31/15, A61K 31/165, A61K31/17, A61K 31/33,  
According to International Patent Classification (IPC) or to both national classification and IPC A61P 3/04, A61P 3/10

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9901423 A1 (NOVO NORDISK A/S ET AL), 14 January 1999 (14.01.99) --	1-88
A	EP 0847992 A1 (MITSUI CHEMICALS, INC.), 17 June 1998 (17.06.98) --	1-88
A	EP 0000816 A1 (BEECHAM GROUP LIMITED), 21 February 1979 (21.02.79) -- -----	1-88

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

22 Sept 2000

Date of mailing of the international search report

27-09-2000

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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/DK00/00264

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 87-88  
because they relate to subject matter not required to be searched by this Authority, namely:  
**See extra sheet\***
2. ☒ Claims Nos.: 1-58, 69-88  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
**See extra sheet\*\***
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.



INTERNATIONAL SEARCH REPORT

International application No.  
PCT/DK00/00264

\*Claims 87-88 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/ Rule. 39.1.(iv).

Nevertheless, a search has been executed for these (this) claim(s). The search has been based on the alleged effects of the compound(s)/composition(s).

\*\*Present claims 1-58 and 69-88 relate to an extremely large number of possible compounds. In fact, the claims contains so many options, variables and possible permutations that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

Consequently, a limited search has been carried out on the basis of claims 59-68.

Claim 5 (when A = -NR<sup>7</sup>-CH<sub>2</sub>-) and claim 9 (A = -NH-CH<sub>2</sub>-) do not seem to be depending on claim 1.

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

01/08/00

International application No.

PCT/DK 00/00264

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